BJA

British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 84 Number 1 January 2000

Editor-in-chief: Jennifer M. Hunter

- Does aprotinin affect renal function during cardiac surgery?
- Allergic reactions to rocuronium
- Woolley and Roe (again)

Journal of the Royal College of Anaesthetists

OXFORD
UNIVERSITY PRESS

Inside you will find technology way ahead of its time
See the Blease Millennium anaesthesia machine in the Dome *Operating Theatre 2010*, London
Blease 8500
QA Photos

P25,795

8500

Anaesthesia ventilation for the new millennium

It's here. A user definable, intuitive and advanced anaesthesia ventilator to take you into the 21st century.

Providing the most comprehensive range of functions, the 8500 is the benchmark by which all other ventilators will be measured.

Ergonomically designed with a tilt screen display, the 8500 is multi-lingual and offers individually tailored and retrievable settings.

It simply has everything you need for safe, accurate and advanced anaesthesia ventilation for years to come.

And with Blease behind it you can be assured that the 8500 will also be both cost-effective and consistently reliable.

For the inside story on the new 8500 talk to **Blease**

Inspired thinking in healthcare

SIMV

Integrated Spirometry

Volume Ventilation

Inspiratory Pause

Electronic PEEP

Spontaneous Ventilation

Pressure Support

Sigh Function

Blease Beech House Chiltern Court Asheridge Road Chesham Bucks HP5 2PX England
Telephone: 01494 784422 (International +44 1494 784422) Facsimile: 01494 791497 (International +44 1494 791497)
e-mail: BleaseSales@compuserve.com Web site: www.blease.co.uk

BJA
International Journal of Anaesthesia
Volume 84 Number 1 January 2000

46

EDITORIAL

1 I: A shame about the patient?
P. M. Hopkins

3 II: Aprotinin and renal function in patients undergoing cardiac surgery
W. H. Hörl

CLINICAL INVESTIGATIONS

6 Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients
P. S. Myles, D. L. Williams, M. Hendrata, H. Anderson and A. M. Weeks

11 Validity and reliability of a postoperative quality of recovery score: the QoR-40
P. S. Myles, B. Weitkamp, K. Jones, J. Melick and S. Hensen

16 Aprotinin does not impair renal haemodynamics and function after cardiac surgery
A. Schweizer, L. Höhn, D. R. Morel, A. Kalangos and M. Licker

23 A placebo-controlled study of the effects of dopexamine on gastric mucosal perfusion in infants undergoing hypothermic cardiopulmonary bypass
P. D. Booker and M. Pozzi

28 Effects of changes in packed cell volume on the specific heat capacity of blood: implications for studies measuring heat exchange in extracorporeal circuits
A. S. T. Blake, G. W. Petley and C. D. Deakin

33 Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients
O. Detsch, G. Schneider, E. Kochs, G. Hapfelmeier and C. Werner

38 Behaviour of near-infrared light in the adult human head: implications for clinical near-infrared spectroscopy
A. E. R. Young, T. J. Germon, N. J. Barnett, A. R. Manara and R. J. Nelson

43 Rocuronium potency and recovery characteristics during steady-state desflurane, sevoflurane, isoflurane or propofol anaesthesia
M. Bock, K. Klippel, B. Nitsche, A. Bach, E. Martin and J. Motsch

48 Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis
L. A. Smith, D. Carroll, J. E. Edwards, R. A. Moore and H. J. McQuay

59 Hyperbaric bupivacaine for spinal anaesthesia in 7–18 yr old children: comparison of bupivacaine 5 mg ml^{-1} in 0.9% and 8% glucose solutions
H. Kokki and H. Hendolin

63 Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children
T. Katoh, S. Kobayashi, A. Suzuki, S. Kato, T. Iwamoto, H. Bito and S. Sato

LABORATORY INVESTIGATION

67 Microdialysis study of the blood-brain equilibration of thiopental enantiomers
L. E. Mather, S. R. Edwards, C. C. Duke and M. J. Cousins

REVIEW ARTICLE

74 Gastrointestinal luminal $P\text{CO}_2$ tonometry: an update on physiology, methodology and clinical applications
J. J. Kolkman, J. A. Otte and A. B. J. Groeneveld

SHORT COMMUNICATIONS

87 Wound infiltration with bupivacaine after surgery to the cervical spine using a posterior approach
L. H. Pobereskin and J. R. Sneyd

89 Comparison of 1% ropivacaine with 0.75% bupivacaine and 2% lidocaine for peribulbar anaesthesia
G. Nicholson, B. Sutton and G. M. Hall

92 Effects of respiratory and metabolic pH changes and hypoxia on ropivacaine-induced cardiotoxicity in dogs
J. M. Porter, F. Markos, H. M. Snow and G. D. Shorten

95 I.v. regional diamorphine for analgesia after foot surgery
M. G. Serpell, E. Anderson, D. Wilson and N. Dawson

97 Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers
T. M. Buetler, O. H. G. Wilder-Smith, C. H. Wilder-Smith, S. Aebi, T. Cerny and R. Brenneisen

100 Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation
A. P. Hall, J. P. Thompson, N. A. P. Leslie, A. J. Fox, N. Kumar and D. J. Rowbotham

103 Comparison of laryngeal mask and intubating laryngeal mask insertion by the naïve intubator
A. Choyce, M. S. Avidan, C. Patel, A. Harvey, C. Timberlake, N. McNeilis and E. Gluckman

106 Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment
K. F. Cheong and W. H. Wong

CASE REPORTS

108 Histaminoid reactions associated with rocuronium
S. McD. Neal, P. R. Manthri, V. Gadiyar and J. A. W. Wildsmith

112 Fatal paradoxical air embolism during liver transplantation
L. Olmedilla, I. Garutti, J. Pérez-Peña, J. Sanz, E. Teigell and M. Avellanal

115 Tension pneumocephalus after neurosurgery in the supine position
G. C. Satapathy and H. H. Dash

118 Severe vasovagal attack during regional anaesthesia for Caesarean section
E. J. Watkins, M. Dresner and C. E. Calow

HISTORY

121 The Woolley and Roe case
J. R. Maltby, C. D. D. Hutter and K. C. Clayton

127 CORRESPONDENCE

129 BOOK REVIEWS

130 ERRATUM

131 EXTENDED GUIDE TO CONTRIBUTORS

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, and the Society for Ambulatory Anesthesia

EDITORIAL

1337 Postoperative Nausea and Vomiting: Prophylaxis vs Treatment

AMBULATORY ANESTHESIA (Society for Ambulatory Anesthesia)

1340 Ondansetron and Breast Surgery
1346 Preoperative Anxiety: Anesthetic Requirements
1352 Prolonged Stay After Ambulatory Surgery

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

1360 Nitric Oxide and Cardiopulmonary Bypass
1366 Interscalene Cervical Block for Carotid Surgery
1371 Controlled Hypotension and Splanchnic Perfusion
1378 Epidural Anesthesia, Splanchnic Perfusion
1382 Blood Loss and Tranexamic Acid vs Acute Normovolemic Hemodilution
1388 Hypotension and Angiotensin II Receptor Antagonists
1393 E 047/1 Effects on Postischemic Arrhythmia
1400 Halothane and Arterial Myogenicity
1406 Emergent Bedside Transesophageal Echocardiography in the Resuscitation of Sudden Cardiac Arrest After Tricuspid Inflow Obstruction and Pulmonary Embolism (Case Report)
1409 Response to Electroconvulsive Therapy in a Quadriplegic Patient (Case Report)

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

1411 Propofol in Children with Heart Disease
1417 Ketamine, Calcium, and Cardiomyocytes
1423 Cardiac Arrhythmias in Pediatric Anesthesia (Brief Communication)
1426 Single-Lung Ventilation in Pediatric Patients (Brief Communication)

CRITICAL CARE AND TRAUMA

1430 Effects of Dopamine After Cardiopulmonary Resuscitation with Vasopressin

NEUROSURGICAL ANESTHESIA

1437 Cerebrovascular CO_2 Reactivity
1442 Isoflurane Reduces Cortical *N*-Methyl-D-Aspartate Toxicity

OBSTETRIC ANESTHESIA

1448 Thiosulfate and Fetus
1453 Modified Thromboelastography in Obstetrics
1456 Amniotic Fluid Embolism-Early Findings of Transesophageal Echocardiography (Case Report)
1459 Gabapentin Therapy for Vulvodynia (Case Report)

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

1461 Ropivacaine Wound Infiltration for Major Shoulder Surgery
1467 Needle Insertion Site for Femoral Nerve Block
1471 Ropivacaine for Ilioinguinal Blocks
1475 Effect of Nerve Block on Hyperalgesia
1482 Tourniquet Leakage in Forearm vs Arm IV Regional Anesthesia
1487 Clonidine and Epidural Morphine
1492 Chronic Epidural Catheterization in Rats
1497 Patient-Controlled Epidural Analgesia Levobupivacaine
1504 Epidural Levobupivacaine and Morphine
1510 Ropivacaine and Spinal Pial Vessels
1514 Combined Stellate Ganglion Blockade and PGE_1
1517 Linearity of the Pain Visual Analog Scale
1521 Effects of Intradermal Fentanyl and Ketamine
1528 Citation Analysis of Pain Literature
1534 Analgesia by Systemic AMPA Antagonist
1538 Identification of a New Therapeutic Approach for Iliac Crest Donor Site Chronic Pain (Case Report)

GENERAL ARTICLES

1541 Hypothermia and Thermostat™ Rewarming
1546 Effects of Hypothermia on a Human Glial Glutamate Transporter
1551 Thermogenesis During Anesthesia Shortens Hospital Stay
1557 Propofol and Diaphragmatic Contractility
1561 Remifentanil's Effect on Biliary Drainage
1565 Interaction Between Ulinastatin and Vecuronium

TECHNICAL COMMUNICATION

1570 Bacterial Growth in Glyceryl Trinitrate and Sodium Nitroprusside

CASE REPORTS

1573 Lingual Hematoma as a Potential Cause of Upper Airway Obstruction
1576 An Unexpected Complication During Laparoscopic Herniorrhaphy
1579 Increased Plasma Cholinesterase Activity and Mivacurium Resistance: Report of a Family
1583 A Case of Nasogastric Tube Knotting Around a Tracheal Tube: Detection and Management
1585 LETTERS TO THE EDITOR
1593 BOOK AND MULTIMEDIA REVIEWS

SPA PRECONVENTION ISSUE

INFOR

ISSN 0003-2999 Volume 89, Number 6, December 1999

Q T A

British Journal of Anaesthesia

Editorial Board

Editor-in-Chief

J. M. HUNTER, Reader in Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Senior Lecturer in Anaesthesia, *University of Leeds*
D. G. LAMBERT, Senior Lecturer in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. R. ELLIS, Professor of Anaesthesia, *University of Leeds*
W. FITCH, Professor of Anaesthesia, *University of Glasgow*
G. M. HALL, Professor of Anaesthesia, *University of London*
D. J. HATCH, Portex Professor of Anaesthesia, *University of London*
P. HUTTON, Vice-president, *Royal College of Anaesthetists*
R. D. MILLER, Professor of Anaesthesia, *University of California, San Francisco*
I. POWER, Associate Professor, *University of Sydney, Australia*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. SEAR, Clinical Reader in Anaesthesia, *University of Oxford*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Reader in Anaesthesia, *University of Plymouth*
L. STRUNIN, President, *Royal College of Anaesthetists*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Technical Editor

LINDA GOUGH

Please visit the Journals's World Wide Web site at http://bjanaes.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to BJA comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate

Institutions: UK and Europe £217, Rest of World US$346
Trainees: UK and Europe £105, Rest of World US$168
Single issue: UK and Europe £23, Rest of World US$36

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express, Diners, JCB); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; Email: jnl.info@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 78 onwards to* Oxford University Press. *For Vols 1–77* to Dawsons Back Issues, Cannon House, Folkestone, Kent. Tel: +44 (0)1303 850101; Fax +44 (0)1303 850440.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)181 786 7376; Fax: +44 (0)181 786 7262.

© *The Board of Management and Trustees of the British Journal of Anaesthesia* 2000

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$322. British Journal of Anaesthesia is distributed by Mercury International, 365 Blair Road, Avenel, New Jersey, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

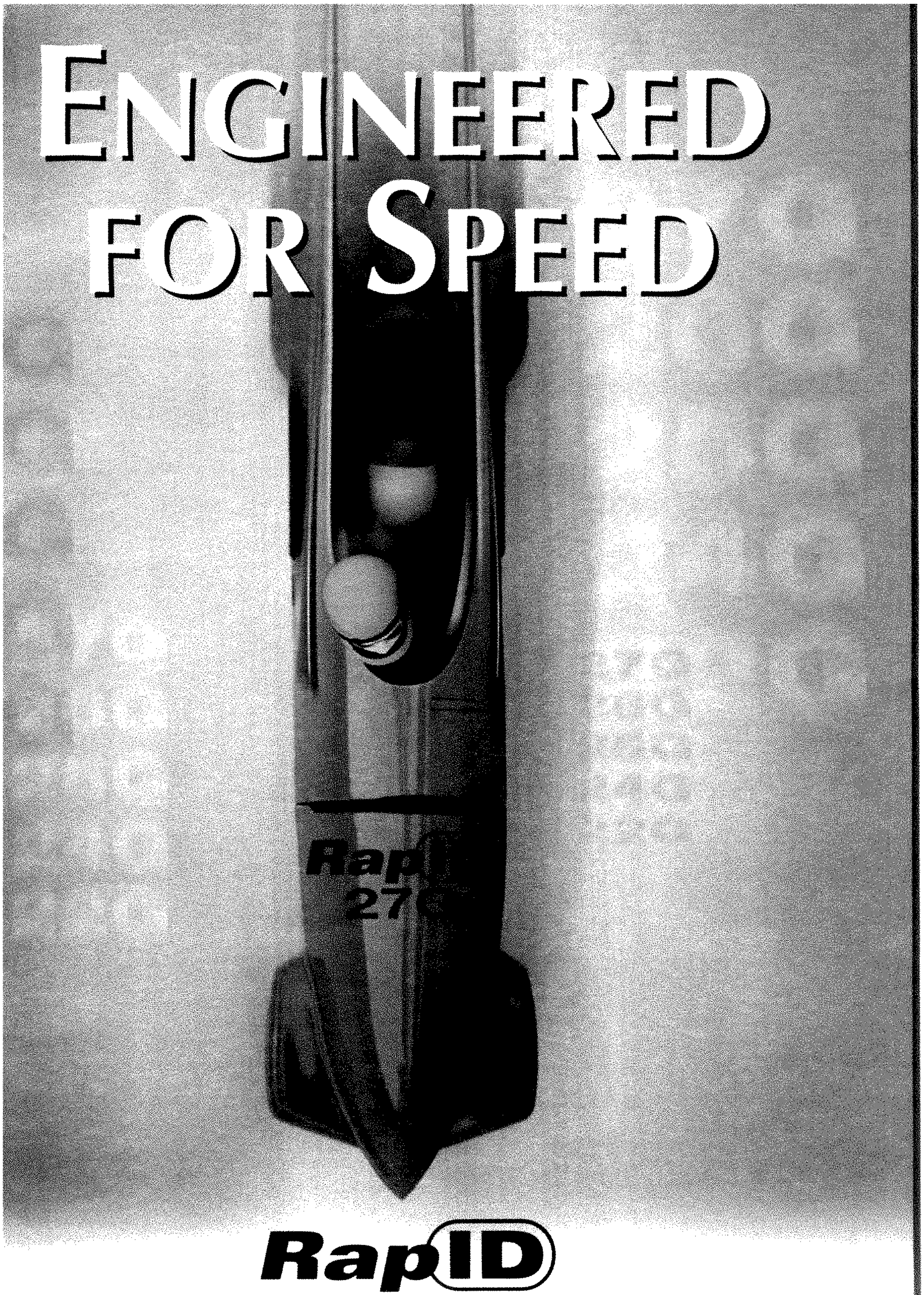
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000



RapID

SUPERIOR FLASHBACK[1] SPINAL NEEDLES

- Improved design for superior flashback[1]
- New 27G addition to range
- Available as pencil point and lancet point

SIMS Portex

rmation, please call SIMS Portex on +44 (0) 1303 260551. SIMS Portex Limited, Hythe, Kent, CT21 6JL, UK.
E-mail: info@portex.com

1. Correspondence held on file, SIMS Portex 1996

SIMS is a world leading medical manufacturing group, with companies in Europe, North America, South Africa and the Pacific region, providing innovative products to critical care and community care professionals worldwide.

SIMS
SMITHS INDUSTRIES
Medical Systems
INNOVATION IN CRITICAL AND COMMUNITY CARE

Patient safety and qualities we value

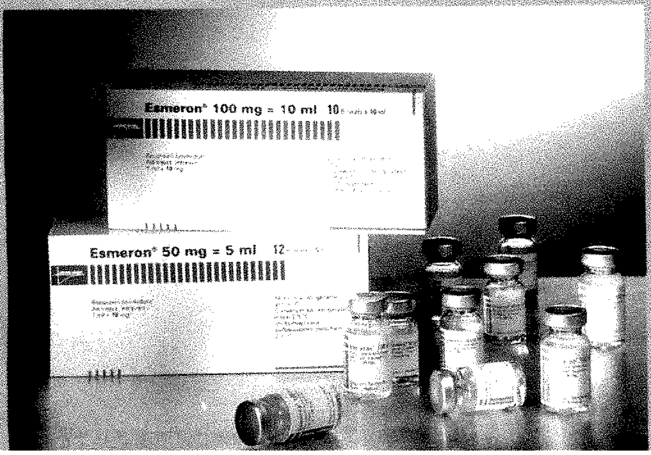
stomer satisfaction ar
ove all others.

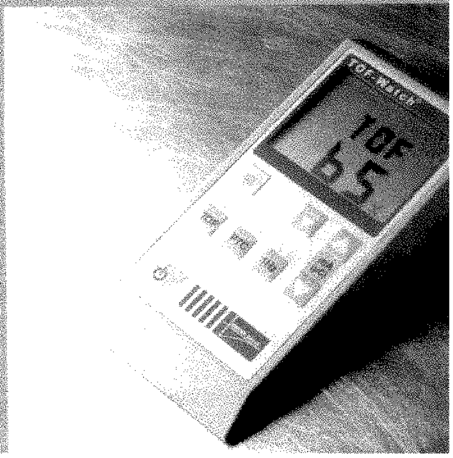
It's our legacy of leadership.

To provide answers to professional needs it is essential to understand them. For more than 3 decades Organon Teknika has been meeting the requirements of anesthesia healthcare teams around the world. That's why our innovative approach to neuromuscular block leads to confident management of muscle relaxation. Moreover, this not only helps to safeguard patients. It also leads to a rational use of neuromuscular blocking drugs giving scope to cost-effective patient management.

Organon Teknika are leaders in neuromuscular block management. Our history of innovation would be envied by any
other. The synergy we initiated between th
of neuromuscular blocking agents and the
toring of its effect is second to none. In thi
Esmeron® (rocuronium bromide) and the
family (TOF-Watch, TOF-Watch S and TC
form a winning combination.

Organon Teknika will continue to underta
development well into the future. Not for t
leader. It is our commitment to meet the e
of our clients. That's the essence of real lea





One Year Obstetric Anesthesia Fellowship

Duke University Medical Center
Durham, North Carolina, USA

Want to get further obstetric anesthesia experience/research and enjoy a good climate/lifestyle? This post is for you. The Department of Anesthesiology at Duke University Medical Center invites applications for Fellowship in Obstetric Anesthesia for the academic year beginning July 2000.

Candidates should have FRCA prior to commencing post. Emphasis on clinical research and advanced clinical training in a tertiary center with approximately 3,000 deliveries per year including many high risk consults and referrals. Opportunities to participate in NIH-funded laboratory research as well as clinical outcomes research. Salary $45,000/annum.

Applicants should send a curriculum vitae and 3 letters of reference to Elizabeth Bell, M.D., M.P.H., Fellowship Director, Division of Women's Anesthesia, Department of Anesthesiology, Box 3094, Duke University Medical Center, Durham, NC 27710. Tel: (919) 681-6535, Fax: (919) 681-8357, E-mail: bell0027@mc.duke.edu

Informal discussion encouraged with either Elizabeth Bell, M.D.; or John Booth, M.B., Ch.B., FRCA, E-mail: booth006@mc.duke.edu

ISMETT*

HEART/LUNG TRANSPLANT ANESTHESIA AT UPMC PALERMO

**(l'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione)*

The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government to be inaugurated during 1999. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@ anes.upmc.edu

11th South West Thames Anaesthesia Update

24-28 Janaury, 2000
Belle Plagne, French Alps

Open to all Anaesthetists - limited to 150 participants

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training & Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers
Videos on New Equipment, Drugs and Techniques

Anaesthetists in training presenting papers are eligible for prizes.
Deadline for abstracts: December 10th 1999

This meeting is approved for CME purposes

For further details, please contact:
Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road,
London SW17 0QT
Fax: 0181 725 3135
Tel: 0181 725 0018
email: liban@mailbox.co.uk
www.mailbox.co.uk/liban/conferences

MID-WESTERN HEALTH BOARD
Republic of Ireland

Registrar in Anaesthetics

Regional General Hospital,
Dooradoyle, Limerick

An immediate vacancy exists.

Please apply by sending CVs to the Personnel Department at the Regional General Hospital. Tel 00 353 61 482 786. Fax 00 353 61 482 644. E-mail cmulcahy@mwhb.ie

All job vacancies can be viewed at our website http://www.mwhb.ie.

This post is open to male and female applicants.

Editorial Notices

Nuffield Trust Announces New £8000 Fellowship

The Nuffield Trust are inviting all readers under the age of 35 yr to apply for the Trust's new Sir Edgar Williams Fellowship which commences at the start of 2000. The successful applicant will be required to spend a 1-month placement in a non-health organization (e.g. airline industry, hotel, media) and to produce a lecture, to be published by the Trust, which considers the advantages of cross-organizational learning. The Fellowship comprises a grant of £3000 plus a travel bursary of up to £5000, sufficient for those interested in a 'working holiday' overseas in 2000. Those interested can find out more information by visiting the Trust's website at www.nuffieldtrust.org.uk, or by telephoning Dr Anne Marie Rafferty on +44 (0)171 927 2305.

Royal Medical Benevolent Fund

The Royal Medical Benevolent Fund reminds readers of its Christmas Appeal. Your generosity last Christmas enabled the Fund to distribute additional seasonal support of £50,000 to help bring some semblance of happiness and dignity to those doctors, and particularly their bereaved families, less fortunate than us. Each year our general grants total over £800,000. The Fund always seeks to give this extra help at Christmas with gifts to the children involved.

Contributions marked "Christmas Appeal" may be sent to the Chief Executive Officer of the RMBF at 24 King's Road, Wimbledon, London SW19 8QN or to the Treasurer of your local guild of this Fund.

BJA/RCA Research Fellowships

The *British Journal of Anaesthesia*, in conjunction with the Royal College of Anaesthetists, is making a further round of grants available to support research in anaesthesia, intensive care or pain relief. The work must be conducted in the UK.

These fellowships are available to support specific research projects in anaesthesia or related departments; research involving the application of basic science to anaesthesia will be preferred. We are looking for applications for fellowships (for at least 1 year in the first instance, but which may be extended for a second year). These are suitable for an anaesthetist at the specialist registrar level. Applicants will preferably be a fellow of the Royal College of Anaesthetists.

Please note that the *BJA*/RCA will not be funding project grants with this round of awards.

For further details and forms, please **WRITE** to:

Dr J.W. Sear (BJA Grants Officer), Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Closing date for applications is **February 29, 2000.** Late applications *will not* be considered

12th International Symposium on Anesthesia and Intensive care

Tel Aviv, Israel, December 7–9, 1999

The symposium is organized by the Division of Anesthesiology of Soroka Center and Ben-Gurion University of the Negev. A full programme of anaesthia and intensive care topics will be presented.

For further information, please contact the Secretariat:

Target Tours, PO Box 29041, Tel-Aviv 61290, Israel.

Tel: +972 3 5175150; Fax: +972 3 5175155; E-mail: trgt@netvision.net.il

18th Annual Symposium: Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

Acapulco, Mexico January 15–22, 2000

Abstract, poster and free papers information
(*deadline – November 1, 1999*):
Helen Phillips, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1010, New York, NY 10029–6574, USA.
Tel: +1 212 241 7467; Fax: +1212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

Symposium on Paediatric Cardiac Anaesthesia and Intensive Care

London, January 17, 2000

The meeting will take place at the Royal Society of Medicine, London.

For further information, please contact:

Dr Adarsh B. Lal, Consultant Anaesthetist, HCI International Medical Centre, Beardmore Street, Clydebank G81 4HX, UK.

Tel: +44 141 951 5612; Fax: +44 141 951 5603; E-mail: adarsh.lal@hci.co.uk

Abu Dhabi 2000

6th Pan Arab Congress on Anaesthesia, ICU, Pain, Emergency and Disaster Medicine
Abu Dhabi, January 17–21, 2000

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

COR-H65512-46-R25795

For further information, please contact:

Secretary General: Dr Murtada Afifi, PO Box 7618 Abu Dhabi, UAE. Tel: 340947–747993–050 6114616; Fax 971 2 311328. E-mail: drafifi@emirates.net.ae.

Seventh Annual Paediatric Anaesthesia Update

Manchester, January 21, 2000

This highly successful CME approved course will take place at the Manchester Conference Centre, Weston Building, Sackville Street, Manchester with a new selection of topical reviews. The course is intended for all consultant and trainee anaesthetists with an interest in paediatric anaesthesia.

For further information, please contact:

Claire Smith, University Department of Anaestheisa, Manchester Children's Hospitals NHS Trust, Hospital Road, Pendlebury, Manchester M27 4HA.

Tel/Fax: +44 (0)161 727 2291.

11th South West Thames Anaesthesia Update

Belle Plagne, French Alps, January 24–28, 2000

Open to all anaesthetists, limited to 150 participants. The scientific programme will include lectures, and discussions on: acute and chronic pain; paediatric update; day care anaesthesia; obstetric anaesthesia; neurology and anaesthesia; ITU and relevant medical topics; cardiothoracic topics; radiology for anaesthetists; new drugs update; training & education; anaesthetic audit; free papers; panel discussions; and workshops.

Deadline for abstracts is December 10, 1999.
This meeting is approved for CME purposes.

For further details, please contact:

Dr J.B.Liban, Department of Anaesthesia, St George's Hospital, Blackshaw Road, London SW17 0QT, UK.

Tel: +44 (0)181 725 0018; Fax: +44 (0)181 725 3135;
E-mail: libian@mailbox.co.uk
www.mailbox.co.uk/libian/conferences

Third International Symposium on Coma and Death

Havana, Cuba, February 22–25, 2000

The symposium will take place at the Havana International Congress Centre.

For further information please contact:

Dr Calixto Machado, Presidente del Simposio, III Simposio Internacional Sobre la Coma et la Muerte, Apartado Postal 4268, La Habana, 104000, Cuba.

Tel: +537 55 3022 (ext. 18); Fax: +537 21 9496/22 8382;
E-mail: braind@informed.sld.cu

European Society of Regional Anaesthesia 3rd Workshop 'Neural blockades on cadavers'

Innsbruck, Austria, February 24–26, 2000

The workshop will be held in the Institute of Anatomy of the University of Innsbruck.

For further details, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Global Update on Pain and 15th National Conference of the Indian Society for the Study of Pain

India, February 11–13, 2000

The conference will be held at the S.P. Jain Auditorium of Bombay Hostital, Mumbai, under the auspices of Bombay Hospotal Institute of Medical Sciences, Mumbai, India.

The Academic Co-Spondor is the World Foundation of Pain and Research Inc., New York, USA. UICC had also granted its support for this Global Update.

For further information, please contact:

Dwarkadas Baheti, Secretary General, GL-UP-NC-ISSP-2000, 15th Floor, MRC, Bombay Hospital, 12 New Marine lines, Mumbai-400 020, India.

Fax: +91 22 208 0871; E-mail: globalpain2000@hotmail.com.

Primary FRCA Revision Course

Leicester, UK, March 6–8, 2000

This course will take place in the Hermitage Hotel, Oadby, Leicester. It is a 3-day residential revision course with 50% of course time on mock exam practice. The co-ordinator is Dr Donal Buggy.

For further information, please contact:

Mrs Anne Henry, University Department of Anaesthesia, Leicester General Hospital, Leicester LE5 4PW, UK.

Tel: +44 (0) 116 258 4661; Fax: +44 (0) 116 258 4611.

6th America–Japan Anesthesia Congress

Honolulu, Hawaii, March 9–10, 2000

74th Clinical and Scientific Congress of the International Anesthesia Research Society

Honolulu, Hawaii, March 10–14, 2000

75th Clinical and Scientific Congress of the International Anesthesia Research Society

Ft. Lauderdale, Florida, March 16–20, 2001

76th Clinical and Scientific Congress of the International Anesthesia Research Society

San Diego, California, March 16–20, 2002

For further information contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131-2553, USA.

Tel: +1216 642 1124; Fax: +1216 642 1127;
E-mail: iarshq@iars.org; Web: www.iars.org

20th International Symposium on Intensive Care and Emergency Medicine

Brussels, March 21–24, 2000

For further information, please contact:

Mr Carl Vanhaesendonck, Manager, Promotion des Soins Intensifs, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Bruxelles, Belgium.

Tel: +32 2 555 3216; Fax: +32 2 555 4555;
E-mail: sympicu@ulb.ac.be

Anaesthetics Refresher Course

Cape Town, March 25–26, 2000

This meeting will take place at the Education Building, University of Cape Town, South Africa.

For further information, please contact:

Mrs J. Theron, Postgraduate Conference Division, Barnard Fuller Building, UCT Faculty of Medicine, Anzio Road, Observatory 7925, Cape Town, South Africa.

Tel: +27 21 406 6911; Fax: +27 21 448 6263.

South African Society of Anaesthesiologists Congress

Cape Town, March 26–30, 2000

This meeting will take place at the Baxter Theatre Complex, Rondesbosch, Cape Town.

For further information, please contact:

Mrs J. Theron, Postgraduate Conference Division, Barnard Fuller Building, UCT Faculty of Medicine, Anzio Road, Observatory 7925, Cape Town, South Africa.

Tel: +27 21 406 6911; Fax: +27 21 448 6263.

8th Annual Congress of the European Society of Anaesthesiologists

Vienna, Austria, April 1–4, 2000

The congress will be held in the Austria Center.

Abstract deadline is December 1, 1999.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Diagnostic Imaging of the Shoulder, Elbow and Wrist Joints: A Radioclinical Challenge

Genval (Brussels), April 28–29, 2000

The symposium is sponsored by the GETROA (Groupe d'Etude et de Travail en Ostéo-Articulaire). The specific aims of the symposium are: to summarize the current state of knowledge on shoulder, elbow and wrist imaging using state-of-the-art techniques; to establish consensual algorithmic approaches for diagnosing of upper extremity pathology, formulating on this basis recommendations to the medical community; to discuss unsolved clinical problems and potential solutions based on current clinical and imaging knowledge; and to explore future directions of investigations.

December 31, 1999 (deadline for submission of abstracts).

For further information, please contact:

F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium.

Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail: fschuind@ulb.ac.be

German Congress of Anaesthesiology 2000

Munich May 6–9, 2000

For further information, please contact:

Nadja Schwarz, Project Managment, Medizinische Congressorganisation Nürnberg GmbH, Wielandstraße 6, D-90419 Nürnberg, Germany.
Tel: +49 911 39 3160; Fax: +49 911 33 1204; E-mail: mcn@mcn.nuernberg.de
www:http//www.mcn-nuernberg.de

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

World Paediatric Anaesthesia Meeting

Nova Scotia June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

New Perspectives in Pain Relief

Leicester, September 21–22, 2000

The Department of Anaesthesia and Pain Management, University of Leicester, in association with the *British Journal of Anaesthesia*, will be holding a meeting on new perspectives in pain relief.

The meeting coincides with 21st anniversary of the founding of the Academic Department of Anaesthesia in Leicester.

For further information, please contact:

Mrs C Gethins, University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Tel: +44 (0) 116 258 5291; Fax: +44 (0) 116 285 4487.

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl.

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)
Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg June 13–16, 2001

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

McMaster University
Hamilton, Canada

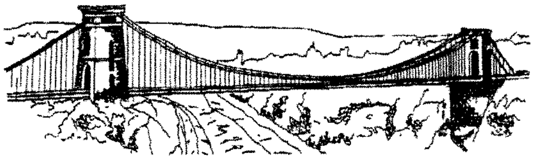
Cardiac Anaesthesia Fellowship

Applications are invited for a Cardiac Anaesthesia Fellowship at Hamilton Health Sciences Corporation, a tertiary regional cardiac centre serving an area from the Niagara Pennisula to the Bruce Peninsula as well as Northwestern Ontario. Annual cardiac surgical volume is over 1,300, providing a full range of cardiac surgical procedures.

Further information is available on the website:

http://www-fhs.mcmasterm.ca/anaesthesia/education
or from Mrs Mary Gahagan, Office of the Chair,
Department of Anesthesia, McMaster University,
HSC-2U1, 1200 Main St W, Hamilton,
Ontario, Canada L8N 3Z5
Tel: 01-905-521-2100 ext. 75166
Fax: 01-905-523-1224
E-mail: gahaganm@fhs.mcmaster.ca

BRISTOL ROYAL HOSPITAL FOR SICK CHILDREN



A SOUTHWEST PAEDIATRIC ANAESTHETIC SYMPOSIUM.

A Symposium of Interest and Relevance to Consultants and SpR's Involved in Anaesthetising Paediatric Patients.

CME approved

THE WATERSHED CONFERENCE CENTRE, BRISTOL
Thursday 25th & Friday 26th May 2000.

GUEST LECTURERS: Dr P. Lonnqvist. Stockholm, Sweden
Dr H. Munro. Michigan, Ann Arbor, USA.

SYMPOSIUM DINNER/DANCE

TRADE EXHIBITION

Registration form from:-
Dr G. R. Lauder
c/o The Anaesthetic Department
St Michael's Hospital
Bristol BS2 8EG
Tel: 0117-928 5203 Fax: 0117-928 5209
E-mail: 113163.2270@compuserve.com

PORTIUNCULA HOSPITAL
BALLINASLOE, IRELAND
A UNIVERSITY AFFILIATED TEACHING HOSPITAL

WESTERN HEALTH BOARD

Portiuncula Hospital,
in conjunction with Roscommon Hospital
wishes to appoint a

CONSULTANT ANAESTHETIST

On a Category 1 basis from July 2000

The appointment will involve a major commitment to Portiuncula Hospital with some sessions at Roscommon Hospital.

This is a new post and the appointee will be expected to demonstrate a part time interest in intensive care.

The following professional qualifications and experience shall apply to this appointment.

(a) Full registration in the General Register of Medical Practioners or entitlement to be so registered.

AND

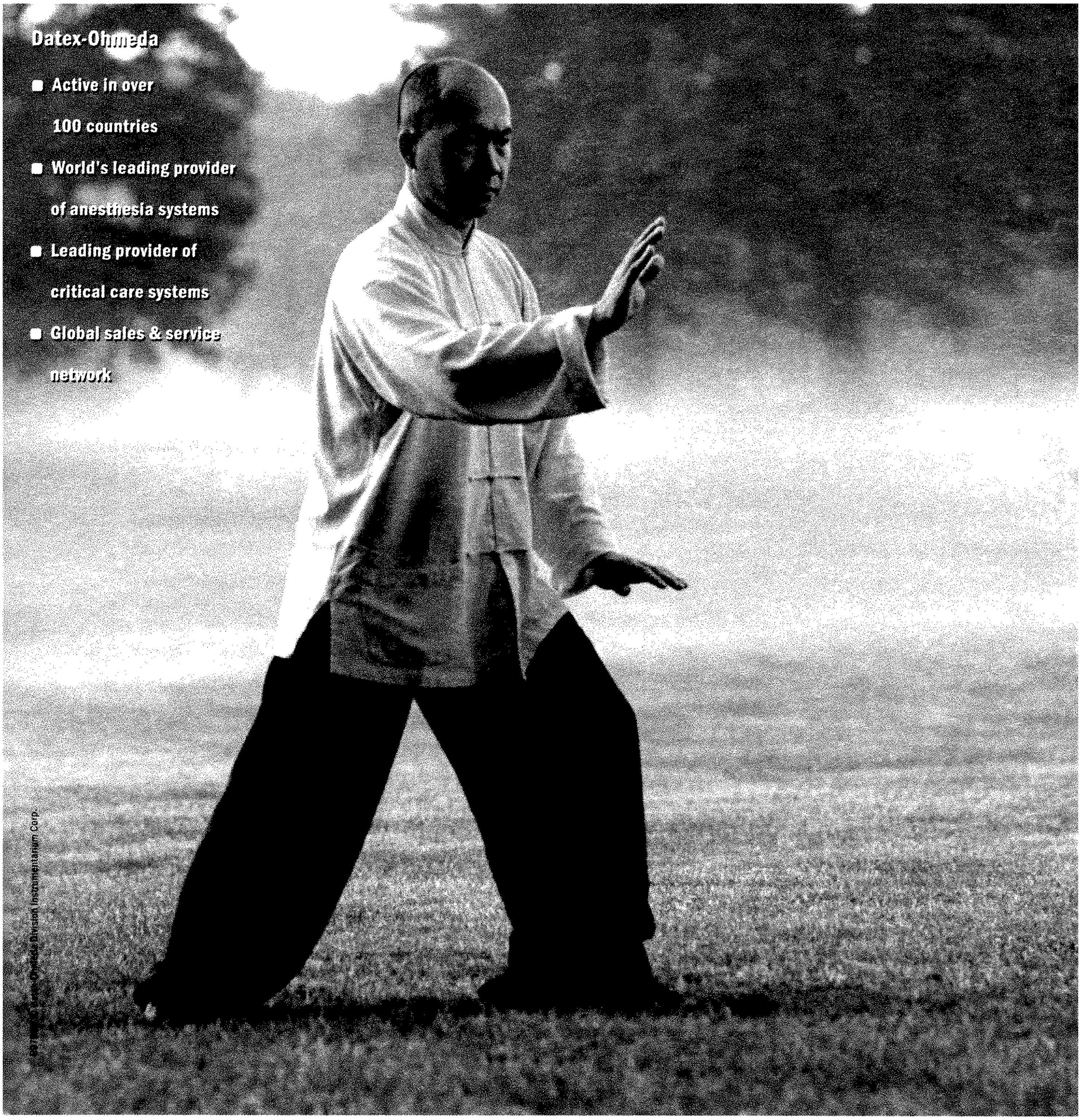
(b) The possession of the Fellowship of the Faculty of Anaesthetists of one of the Royal Colleges of Surgeons or a qualification in anaesthesia at least equivalent thereto

AND

(c) At least six years satisfactory experience (after primary medical qualification) in the practice of the medical profession including specialisation on a full-time basis, in the practice of anaesthesia for a period of at least five years including at least one year's satisfactory experience in intensive care.

Candidates should forward 2 copies of their CV's to The Personnel Manager, Portiuncula Hospital to arrive not later than Monday January 24th 2000.

We are an equal opportunities employer and offer a smoke-free working environment.


Datex-Ohmeda
Active in over 100 countries
World's leading provider of anesthesia systems
Leading provider of critical care systems
Global sales & service network
[illegible] Datex-Ohmeda Division Instrumentarium Corp.

Devoted to life's balance

Life goes up and down. Living is about finding a balance, losing it, and finding it again. So that we become wiser as the years go by. For over 100 years, we have been devoted to the growth of healthcare. To finding its balance.

We are Datex-Ohmeda.

Our products help healthcare professionals reach the goal – preserving life. This is why we are the world's leading provider of anesthesia systems. And an important provider of critical care systems. We are now ready to make anesthesia and critical care work as one – solutions at the heart of the entire care process.

Datex·Ohmeda

Devoted to caring for life

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 84, Number 1, January 2000

Editorial I

A shame about the patient?

We have all heard a variant of the old medical joke in which the elated surgeon proudly proclaims his operation to be 'a great success', but then adds in a quieter and sombre tone '...but it is a shame about the patient'. The best humour works because it is often based on observation of real events. To anaesthetists, the concept of a surgeon blinded to everything but his technical achievement is one with which we can relate. But before we content ourselves with our amusement at this stereotypical surgeon, perhaps we should look for similar tendencies in our anaesthetic practice.

One of my early anaesthesia teachers instilled in me the satisfaction of providing a good anaesthetic. But what is a good anaesthetic? We can cite various factors: before operation, all potential problems were identified; cannulae were sited at the first attempt; induction was smooth, with no coughing, laryngeal spasm or abnormal movements; airway instrumentation was achieved without trauma; haemodynamic variables were stable throughout; surgical conditions were ideal; the patient awakened promptly after discontinuation of anaesthesia and soon met the criteria for discharge from the post-anaesthesia care unit, etc. These are worthy *technical* objectives but are irrelevant to the patient whose anxiety before operation was unrelieved, who recalls the laryngoscope being put in their mouth, who after operation could not move in bed without experiencing excruciating pain, who vomits repeatedly, who has painful thrombophlebitis, who is immobilized for several days by succinylcholine myalgia, or even one who feels restless and is unable to concentrate. Without relevant measures of outcome, it is fruitless to attempt any assessment of quality.

We must also ensure that our clinical decisions are based on research in which relevant measures of outcome are used. A recent study reported that the majority of decisions made during anaesthesia had evidential support.[1] However, little of this evidence demonstrated that the intervention under question improved outcome and even less that it was superior to an alternative intervention. The limitations of the evidence-base for anaesthesia explain the huge variation in anaesthetic technique and choice of drugs used by different anaesthetists for similar cases.

The most important outcomes of anaesthesia, that the patient survives and that they do so without lasting disability, are easy to agree and to measure. However, the low frequency of death and major morbidity requires very large samples for study of factors affecting them or their audit. A recent editorial[2] argued for the necessity of large randomized studies to address these important issues in anaesthesia.

Two studies reported in this issue of the *British Journal of Anaesthesia*[3 4] are concerned with the patient's perception of their care as a measure of outcome. The first is a prospective, observational study involving more than 10 000 patients.[3] It examines the incidence of patient satisfaction after anaesthesia and surgery, together with an analysis of factors associated with dissatisfaction. The data are fascinating. For example, pain in the immediate postoperative period is associated with a rate of dissatisfaction twice that associated with subsequent pain. It is also an interesting (but not strictly valid) exercise to identify those at greatest risk of dissatisfaction as young, healthy women undergoing elective surgery of relatively short duration. Above all, however, this study illustrates an apparent cumulative effect of the number of complications on patient dissatisfaction. Thus a study comparing two analgesic regimens, A and B, might conclude that A is superior to B because of a statistically significant 25-mm reduction in median pain score and yet miss the fact that patients receiving A had a greater incidence of dissatisfaction because of nausea and vomiting, headache, confusion and urinary retention. While confirming pain, nausea and vomiting, awareness and other complications as useful quality indicators, the work of Myles and colleagues[3] illustrates patient satisfaction as a most clinically relevant, albeit crude, measure of outcome.

The second study, from the same group,[4] addresses the problem of quantification of patient perception of quality of care. It describes the development and evaluation of a scoring system for quality of recovery after anaesthesia and surgery. Such scoring systems that are of proven validity and are reproducible both within and between groups, are essential if these outcomes are to be comparable between cohorts for research and audit purposes. The next stage in the development of this scoring system is for it to be evaluated in other centres.

Armed with important and relevant measures of outcome, there is much to be done by both the researcher and each hospital department. The research community needs to organize itself to address the issues of safety and quality with large randomized controlled studies.[2] Within each

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

department of anaesthesia, variations from accepted standards of quality of outcome can be examined for likely causes. It is inevitable that one potential factor determining quality of outcome is the anaesthetist. This is a concern to some practitioners, but this perceived threat can be alleviated by ensuring the response to differences in quality outcome between anaesthetists is educational and developmental rather than punitive.

In Britain, quality of health care provision has achieved recent political prominence.[5 6] This has been accompanied by the inevitable jargon. Providers of health care must now demonstrate that they have embraced the requirements of the 'clinical governance agenda'.[6] We await the first pronouncements of the National Institute for Clinical Excellence (NICE). It is easy to be cynical about such developments, but it would be wrong to dismiss the fundamental ideas because of the political packaging. Is this not an opportunity to develop quality assurance procedures that are based on meaningful outcomes? Such opportunities need to be taken while the political will to provide the necessary resources is present. And the additional resources required are substantial. For example, one of the problems in establishing effective quality assurance is determining and implementing the mechanism by which data are collected and analysed: an aim should be to develop a common data collection system across the country, as is occurring in Germany.[7 8]

In summary, if we can define the measures of outcome after anaesthesia that are important indicators of quality, anaesthesia research can be directed towards factors that influence outcome. The outcomes would become indicators of performance by comparison with benchmarks through rigorous quality assurance procedures. Above all, we will know that we are doing our best for our patients.

P. M. Hopkins
Academic Unit of Anaesthesia
St James's University Hospital
Leeds LS9 7TF
UK

References

1 Myles PS, Bain DL, Johnson F, McMahon R. Is anaesthesia evidence-based? A survey of anaesthetic practice. *Br J Anaesth* 1999; **82**: 591–6

2 Myles PS. Why we need large randomized trials in anaesthesia. *Br J Anaesth* 1999; **83**: 833–4

3 Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients. *Br J Anaesth* 2000; **84**: 6–10

4 Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth* 2000; **84**: 11–15

5 Department of Health. *A First Class Service: Quality in the New NHS.* London: Department of Health, 1998 (Health Circular HSC 1998/113)

6 Department of Health. *Clinical Governance: Quality in the New NHS.* London: Department of Health, 1999 (Health Circular HSC 1999/065)

7 Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin. Massnahmen zur Qualitätssicherung von Anästhesieverfahren. *Anästh Intensivmed* 1992; **33**: 78–83

8 Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin. Kerndatensatz Qualitätssicherung in der Anästhesie. *Anästh Intensivmed* 1993; **34**: 331–6

British Journal of Anaesthesia 84 (1): 3–5 (2000)

BJA

Editorial II

Aprotinin and renal function in patients undergoing cardiac surgery

Aprotinin is used routinely in many centres for patients undergoing cardiac surgery. This serine proteinase inhibitor preserves haemostatic function by reducing fibrinolysis and preserving platelet function. Haemorrhage requiring re-exploration after cardiac surgery is associated with markedly increased mortality and duration of stay.[1] Patients undergoing cardiac surgery treated with aprotinin have significantly less total postoperative blood loss and significantly lower transfusion requirements.[2 3] Impairment of renal function and acute postoperative renal failure requiring or not requiring extracorporeal therapy are common complications of cardiac and thoracic aortic surgery. Risk factors for acute postoperative renal failure in thoracic and thoracoabdominal aortic surgery include advanced age, preoperative renal dysfunction, duration of renal ischaemia and amount of blood transfused.[4] There are similar risk factors for patients undergoing cardiac surgery. Therefore, reduction of postoperative blood loss and transfusion requirements should reduce renal complications in patients undergoing cardiac surgery treated with aprotinin. In contrast, renal dysfunction and renal failure have been reported in patients undergoing profound hypothermia and circulatory arrest given high-dose aprotinin therapy.[5 6]

Effect of high-dose aprotinin therapy on renal function in experimental studies

Short-term administration of aprotinin does not affect renal function in normovolaemic rats. However, aprotinin 50 000 kallikrein inhibitory units/kg body weight (kiu kg^{-1}), followed by a continuous infusion of 100 kiu min^{-1} kg^{-1} decreased renal blood flow, glomerular filtration rate, and sodium, potassium and water excretion in volume-expanded conscious animals.[7] These effects of aprotinin have been attributed to inhibition of renal kallikrein and to a decrease in prostaglandins secondary to the decrease in kinins. As both kallikrein and prostaglandin E_2 and I_2 cause afferent renovasodilation, inhibition by aprotinin may result in a decrease in renal blood flow and glomerular filtration rate. Seto and colleagues[8] administered a bolus dose of aprotinin 10 000 kiu kg^{-1} to anaesthetized rats and an infusion of 1000 kiu kg^{-1} min^{-1} for 60 min. Aprotinin caused a significant decrease in renal blood flow and glomerular filtration rate. These changes occurred in the absence of significant changes in either arterial pressure or cardiac output.[8] It was suggested that the decrease in intrarenal formation of kinins may modify renal blood flow and glomerular filtration rate, and that the changes in electrolyte and water excretion may be secondary to the alterations in renal haemodynamics. In canine experiments, infusion of aprotinin 50 000 kiu kg^{-1} caused a transient but significant reduction in sodium reabsorption and reduced potassium excretion without affecting renal blood flow or glomerular filtration rate.[9] These authors concluded that a single infusion of a high dose of aprotinin caused small and transient functional changes in normothermic healthy kidneys. In pigs, high-dose aprotinin therapy has been shown to induce a decrease in renal blood flow during acute stress.[10] Early clinical studies of aprotinin in patients undergoing cardiopulmonary bypass reporting an increase in creatinine clearance, free water and sodium clearance in the first 12–24 h after operation are therefore difficult to interpret.[11 12]

Evidence for significant impairment of renal function by aprotinin during cardiac surgery?

Aprotinin markedly improves haemostasis in patients undergoing cardiac surgery but concerns have been raised about renal dysfunction.[5 6 11–13] Several recent publications have addressed the question of whether a reduction in the dose of aprotinin is effective with respect to haemostatic efficacy, and safe in terms of kidney function. It has been shown that half of the standard dose of aprotinin is effective.[14 15] The study of Hayashida and colleagues demonstrated that minimal-dose aprotinin (1.0×10^6 kiu) inhibited enhanced fibrinolytic activity and reduced blood loss and transfusion requirements after bypass to a similar degree as low-dose aprotinin ($2.7\pm0.5\times10^6$ kiu).[2] In primary valve replacement and reconstruction, postoperative renal dysfunction was observed in 11% of patients treated with high-dose aprotinin, in 7% of those treated with low-dose aprotinin but in none of the placebo patients. However, there was a disproportionate number of patients with diabetes mellitus in the high-dose aprotinin group with postoperative renal dysfunction.[16]

Plasma creatinine values were within the normal range in the study of Lemmer and colleagues but were approximately 0.5 mg dl^{-1} higher in aprotinin-treated coronary artery bypass patients than in those in the placebo group.[17] Increases in serum creatinine concentration occurred after operation in more patients who received aprotinin (20 of 108) than in placebo-treated patients (13 of 108). However, the difference between the groups was not statistically significant, and the increases in serum creatinine were generally transient.[17] An increase in serum creatinine concentration (>0.5 mg dl^{-1}) was also observed in a greater number of aprotinin-treated patients undergoing primary valve replacement and reconstruction compared with placebo-treated patients (30% vs 8 %, respectively). This effect

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Possible risk factors affecting renal function in aprotinin-treated patients undergoing cardiac surgery

Deep hypothermia
Insertion of a left ventricular assist device
Concomitant therapy with nephrotoxic drugs such as aminoglycosides, or afferent renovasoconstrictors such as radiocontrast media or non-steroidal anti-inflammatory drugs
Concomitant therapy with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists
Pre-existing renal disease (e. g diabetic nephropathy)
Pre-existing impaired renal function
High-dose aprotinin therapy in patients with renal risk factors

of aprotinin was also dose-dependent and was related to co-morbidity such as diabetes mellitus.[16] Efficacy and safety studies of aprotinin therapy in North America have shown no overall effect of aprotinin on plasma creatinine.[18] But a significant increase in creatinine concentration outside the normal range has been observed after insertion of a left ventricular assist device.[19]

In this issue, Schweizer and colleagues describe their randomized, double-blind study assessing the perioperative changes in renal haemodynamics and function in patients undergoing cardiac surgery, pretreated (n=28) or not (n=29) with aprotinin (mean dose 4.1 kiu kg^{-1}). Urinary flow, osmolar clearance and fractional excretion of sodium and potassium did not differ between the aprotinin and non-aprotinin groups. The same was true for creatinine clearance, insulin clearance (as markers of glomerular filtration rate) and *para*-aminohippurate clearance (as a marker of effective renal plasma flow).[20]

In the study of Feindt and colleagues, high-dose aprotinin (2 000 000 kiu at induction of anaesthesia, 2 000 000 kiu added to the priming volume of the heart–lung machine, and 500 000 kiu h^{-1} during operation) did not affect serum creatinine (day before vs day after operation) in patients undergoing aortocoronary bypass grafting. However, tubular markers such as α_1-microglobulin were increased significantly in the urine of aprotinin-treated patients at 3 and 5 days after operation. Similarly, the bands of urinary proteins filtered in the renal tubular system, determined by sodium dodecyl sulphate gel electrophoresis, were significantly increased in the aprotinin group.[21]

Conclusion

Aprotinin therapy, even in high doses, does not impair renal haemodynamics and function in the majority of patients undergoing cardiac surgery. If renal dysfunction occurs, it is usually mild and transient. Potential risk factors affecting renal function in aprotinin-treated patients are summarized in Table 1. As aprotinin may occasionally cause afferent renovasoconstriction, concomitant therapy with known afferent renovasoconstrictors such as radiocontrast media or non-steroidal anti-inflammatory drugs should be avoided. A decrease in intraglomerular pressure caused by afferent renovasoconstriction with a decrease in glomerular filtration rate is usually counterbalanced by efferent renovasoconstriction caused by angiotensin II. This leads to normalization of intraglomerular pressure and glomerular filtration rate. If aprotinin is used, concomitant therapy with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists could be harmful. There are some concerns that low-dose or minimal-dose aprotinin therapy is not as effective as high-dose aprotinin treatment with respect to blood loss and coagulation patterns. Nevertheless, low-dose or minimal-dose aprotinin therapy is recommended for at-risk patients until more data are available.

W. H. Hörl
Division of Nephrology and Dialysis,
Department of Medicine III,
University of Vienna,
Währinger Gürtel 18–20,
A-1090 Vienna, Austria

References

1 Dacey LJ, Munoz JJ, Baribeau YR, et al. Reexploration for hemorrhage following coronary artery bypass grafting. *Arch Surg* 1998; **133**: 442–7

2 Hayashida N, Isomura T, Sato T, Maruyama H, Kosuga K, Aoyagi S. Effects of minimal-dose aprotinin on coronary artery bypass grafting *J Thorac Cardiovasc Surg* 1997; **114**: 261–9

3 Ehrlich M, Grabenwoger M, Cartes-Zumelzu F, et al. Operations on the thoracic aorta and hypothermic circulatory arrest: is aprotinin safe? *J Thorac Cardiovasc Surg* 1998; **115**: 220–5

4 Godet G, Fléron MH, Vicaut E, et al. Risk factors for acute postoperative renal failure in thoracic or thoracoabdominal aortic surgery: a prospective study. *Anesth Analg* 1997; **85**: 1227–32

5 Sundt TM, Kouchoukos NT, Saffitz JE, Murphy SF, Wareing TH, Stahl DJ. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. *Ann Thorac Surg* 1993; **55**: 1418–24

6 Westaby S, Forni A, Dunning J, et al. Aprotinin and bleeding in profoundly hypothermic perfusion. *Eur J Cardiothorac Surg* 1994; **8**: 82–6

7 Kramer HJ, Moch T, von Sicherer L, Dusing R. Effects of aprotinin on renal function and urinary prostaglandin excretion in conscious rats after acute salt loading *Clin Sci* 1979; **56**: 547–53

8 Seto S, Kher V, Scicli G, Beierwaltes WH, Carretero OA. The effect of aprotinin (a serine protease inhibitor) on renal function and renin release. *Hypertension* 1983; **5**: 893–9

9 Fischer JH, Knupfer P. Hochdosierte Aprotinin (Trasylol)-Therapie – unschädlich fur die Niere? *Langenbecks Archiv Chirurg* 1983; **360**: 241–9

10 Maier M, Starlinger M, Zhegu Z, Rana H, Binder BR. Effect of the protease inhibitor aprotinin on renal hemodynamics in the pig *Hypertension* 1985; **7**: 32–8

11 Blauhut B, Gross C, Necek S, Doran J, Späth P, Lundsgaard-Anderson P. Effects of high-dose aprotinin and blood loss, platelet function, fibrinolysis, complement, and renal function after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1991; **101**: 958–67

12 Cosgrove DM, Heric B, Lytle BW, *et al* Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992; **54**: 1031–8

13 Westaby S. Aprotinin in perspective. *Ann Thorac Surg* 1993; **55**: 1033–41

14 Kawasuji M, Ueyama K, Sakakibara N, *et al.* Effect of low-dose aprotinin on coagulation and fibrinolysis in cardiopulmonary bypass. *Ann Thorac Surg* 1993; **55**: 1205–9

15 Liu B, Tengborn L, Larson G, *et al.* Half-dose aprotinin preserves hemostatic function in patients undergoing bypass operations. *Ann Thorac Surg* 1995; **59**. 1534–40

16 D'Ambra MN, Akins CW, Blackstone EH, *et al.* Aprotinin in primary valve replacement and reconstruction: a multicenter, double-blind, placebo-controlled trial. *J Thorac Cardiovasc Surg* 1996; **112**: 1081–9

17 Lemmer JH Jr, Stanford W, Bonney SL, *et al.* Aprotinin for coronary artery bypass grafting: effect on postoperative renal function. *Ann Thorac Surg* 1995; **59**: 132–6

18 Smith PK, Muhlbaier LH. Aprotinin: safe and effective only with the full-dose regimen. *Ann Thorac Surg* 1996; **62**: 1575–7

19 Goldstein DJ, Seldomridge JA, Chen JM, *et al* Use of aprotinin in LVAD recipients reduces blood loss, blood use, and perioperative mortality. *Ann Thorac Surg* 1995; **59**: 1063–7

20 Schweizer A, Hohn L, Morel DR, Kalangos A, Licker M Aprotinin does not impair renal haemodynamics and function after cardiac surgery. *Br J Anaesth* 2000; **84**: 16–22

21 Feindt PR, Walcher S, Volkmer I, *et al* Effects of high-dose aprotinin on renal function in aortocoronary bypass grafting *Ann Thorac Surg* 1995; **60**: 1076–80

British Journal of Anaesthesia 84 (1): 6–10 (2000)

BJA

CLINICAL INVESTIGATIONS

Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients†

P. S. Myles*, D. L. Williams, M. Hendrata, H. Anderson and A. M. Weeks

Department of Anaesthesia and Pain Management, Alfred Hospital, PO Box 315, Prahran, Melbourne, Victoria 3181, Australia

**Corresponding author*

Patient satisfaction after anaesthesia is an important outcome of hospital care. We analysed our anaesthetic database to identify potentially modifiable factors associated with dissatisfaction. At the time of analysis, our database contained information on 10 811 in-patients interviewed on the first day after operation. The major subjective outcome measure was patient satisfaction. We also measured other predetermined outcomes, such as nausea, vomiting, pain and complications. The overall level of satisfaction was high (96.8%); 246 (2.3%) patients were 'somewhat dissatisfied' and 97 (0.9%) were 'dissatisfied' with their anaesthetic care. After adjustment for patient and surgical factors, there was a strong relation between patient dissatisfaction and: (i) intraoperative awareness (odds ratio (OR) 54.9, 95% confidence intervals (CI) 15.7–191); (ii) moderate or severe postoperative pain (OR 3.94, 95% CI 3.16–4.91); (iii) severe nausea and vomiting (OR 4.09, 95% CI 3.18–5.25); and (iv) any other postoperative complications (OR 2.04, 95% CI 1.61–2.56). Several factors associated with dissatisfaction may be preventable or better treated.

Br J Anaesth 2000; **84**: 6–10

Keywords: anaesthesia, audit; measurement techniques, outcome; complications, morbidity; research, anaesthesia; surgery, postoperative period

Accepted for publication: June 30, 1999

Quality of health care has been defined as the degree to which health services increase the likelihood of desired health outcome consistent with current professional knowledge.[1 2] Quality of life is relevant in this context and can be measured after anaesthesia and surgery by (i) objective dimensions (desired treatment outcome, functional status) and/or (ii) subjective dimensions, such as assessments of well being (affective component) and patient satisfaction (cognitive component).[3 4] Patient satisfaction is an important measure of quality of care that can contribute to a balanced evaluation of the structure, process and outcome of services.[2 5]

Many factors contribute to patient satisfaction, including accessibility and convenience of services, institutional structure, interpersonal relationships, competence of health professionals and a patient's own expectations and preferences.[6–8] Most patients (85%) expect uneventful anaesthesia.[9] Nevertheless, recovery from anaesthesia and surgery is sometimes complicated by residual sedation, pain, nausea, vomiting and a variety of other major and minor complaints.[10–13]

Satisfaction with health care is usually very high (>85%).[8 14] Consequently, it is difficult to identify a representative sample of patients dissatisfied with care without studying a large population. There are few studies in anaesthesia that have assessed patient satisfaction, and most are restricted to day-case surgical patients.[15–19] We established a postoperative survey of patients on the day after surgery as a quality assurance (QA) activity several years ago to measure patient outcome and our performance.

Methods

Our institution is a 400-bed, adult tertiary care hospital with most types of specialized surgical services, excluding obstetrics and paediatrics. As part of an ongoing quality improvement programme established in 1993 by the Department of Anaesthesia and Pain Management, surgical in-patients are interviewed within 24 h of surgery and

---

†This article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

anaesthesia. Our QA coordinator and/or anaesthetic registrar conducts this formal postoperative review. Patients who receive anaesthesia but recover in locations outside the operating theatre suite (such as angiography, endoscopy or electroconvulsive therapy) do not receive formal postoperative review. Day-case surgical patients are reviewed in the recovery room, but not on the day after surgery (and so are not asked to rate their satisfaction level).

Data collection included patient characteristics, co-morbidities, previous anaesthetic complications, comprehensive anaesthetic details, type of surgery, intraoperative critical events and several predetermined postoperative outcomes. Duration of anaesthesia included preparation, surgery, emergence and transfer to the recovery room. Satisfaction with anaesthesia was included as a subjective outcome. Patients were asked to rate if they were 'satisfied', 'somewhat dissatisfied' or 'dissatisfied' with the anaesthetic service they received. Reasons for patient dissatisfaction were explored at the interview (and, where possible, explanation and/or treatment was provided), but this information was not recorded. Patients who were dissatisfied or somewhat dissatisfied were categorized as dissatisfied for further analysis. Pain control was rated on an ordinal scale and then dichotomized as 1=excellent/good control or 0=adequate/fair–poor control. Nausea and vomiting were rated on an ordinal scale and then dichotomized as 1=severe nausea/vomiting or 0=no nausea/mild nausea. Other postoperative complications included sore throat, headache, soft tissue injury, muscle pain, back pain, urinary retention, confusion, neurological deficit, myocardial infarction, hepatitis and renal failure. These data were entered onto a computer database for future audit. We obtained Ethics Committee approval to access this database for research purposes.

Statistical analysis

Descriptive statistics were derived for the study population and are expressed as number (%) or mean (SD). Associations of categorical variables with patient dissatisfaction were assessed using chi-square tests, and the significance of continuous variables was assessed with *t* tests. Univariate odds ratios (OR) and 95% confidence intervals (CI) were used as estimates of risk for categorical variables. Significant ($P<0.05$) variables were then entered into separate multivariate logistic regression models to calculate adjusted OR. Each model included patient age, sex, ASA status, use of neuromuscular blocking agents and duration of anaesthesia, as it was considered that these factors were clinically significant covariates (patient smoking history and emergency surgery were not statistically significant in the multivariate analysis). Two-way interactions were not explored. All analyses were performed using SPSS v8.0 for Windows. A two-sided P value of <0.01 was used for statistical significance.

Table 1 Patient, anaesthetic and surgical characteristics of the study population (n=10 811) COAD=Chronic obstructive airways disease, ENT=ear, nose and throat

Variable	Number	%
Age group		
<25 yr	1004	9.3
25–34 yr	1319	12.2
35–44 yr	1282	11.9
45–54 yr	1452	13.4
55–64 yr	1757	16.3
65–74 yr	2219	20.5
>75 yr	1778	16.4
Male sex	6399	59.2
ASA status		
I	2092	19.4
II	3715	34.4
III	3805	35.2
IV	1180	10.9
V	19	0.2
Non-elective	1566	14.5
Past medical history		
None	781	7.2
Angina	1938	17.9
Myocardial infarction	1145	10.6
Cardiac failure	900	8.3
Hypertension	2785	25.8
Asthma/COAD	1605	14.8
Diabetes	1089	10.1
Psychiatric	501	4.6
Smoking status		
Nil	6963	64.4
Ex-smoker	2112	19.5
Current smoker	1736	16.1
Neuromuscular blockers	6658	61.6
Laryngeal mask airway	1859	17.2
Intraoperative antiemetic	678	6.3
Epidural–spinal anaesthetic	864	8.0
Type of surgery		
General	2777	25.7
Orthopaedic	2046	18.9
Cardiothoracic	1336	12.4
Neurosurgical	820	7.6
Vascular	784	7.3
Urological	755	7.0
ENT/faciomaxillary	691	6.4
Plastic	578	5.3
Burns	198	1.8
Ophthalmological	135	1.2
Gynaecological	115	1.1
Other	576	5.3

Results

Perioperative data for 17 106 patients were entered onto our QA database, of which 10 811 patients had been reviewed the day after surgery to rate their satisfaction with care (most of the remainder were discharged on the day of surgery, some in-patients were heavily sedated (usually in the ICU) or too confused to participate). The characteristics of the study population are presented in Table 1. Mean duration of anaesthesia was 2.42 (SD 2.2) h. Overall, 85% of operations were elective and neuromuscular blocking agents were used on 62% of occasions. There were 12 (0.11%) episodes of awareness reported after operation.

The overall level of satisfaction was 96.8%; 246 (2.3%) patients were 'somewhat dissatisfied' and 97 (0.9%) were 'dissatisfied' with their anaesthesia care. Patients who were

Table 2 Factors associated with patient dissatisfaction and anaesthesia care (n=10 811). The overall level of dissatisfaction was 3.2%. AMI=Acute myocardial infarction; COAD=chronic obstructive airways disease. *Complications included sore throat, headache, soft tissue injury, muscle pain, back pain, urinary retention, confusion, neurological deficit, myocardial infarction and renal failure (pain, nausea and vomiting have been excluded)

Variable	Incidence (%)	Dissatisfaction rate (%)	Univariate OR (95% CI)	*P*
Age ≥65 yr	37	2.0	0.50 (0.39–0.65)	<0.0005
Female sex	40	4.3	1.78 (1.43–2.21)	<0.0005
ASA status III, IV or V	46	2.6	0.70 (0.56–0.87)	0.001
Non-elective	15	2.4	0.71 (0.50–1.0)	0.048
Past medical history				
None	7.2	4.6	0.70 (0.44–1.14)	0.15
Angina	18	1.6	0.45 (0.31–0.65)	<0.0005
AMI	11	1.5	0.43 (0.26–0.71)	<0.0005
Cardiac failure	8.3	1.4	0.43 (0.24–0.74)	<0.0005
Hypertension	26	2.7	0.79 (0.61–1.02)	0.072
Asthma/COAD	15	3.3	1.05 (0.78–1.41)	0.75
Diabetes	10	1.8	0.54 (0.35–0.86)	0.008
Psychiatric	4.6	4.0	1.29 (0.81–2.04)	0.28
Ex- or current smoker	36	2.7	0.79 (0.63–1.0)	0.05
Neuromuscular blocker	62	2.8	0.74 (0.60–0.92)	0.006
Intraoperative antiemetic	6.3	3.8	1.24 (0.82–1.86)	0.31
Epidural–spinal	8.0	3.2	1.02 (0.69–1.52)	0.91
Any intraoperative adverse event	31	2.5	0.72 (0.57–0.93)	0.011
Recovery room				
Any adverse event	70	3.7	1.79 (1.37–2.33)	<0.0005
Moderate or severe pain	3.8	16.2	7.08 (5.30–9.45)	<0.0005
Severe nausea or vomiting	0.5	10.0	3.43 (1.35–8.69)	0.006
Postoperative review (day after surgery)				
Moderate or severe pain	24	7.3	4.16 (3.34–5.18)	<0.0005
Severe nausea or vomiting	9.7	10.0	4.44 (3.50–5.64)	<0.0005
Awareness	0.11	58.3	43.6 (13.8–138)	<0.0005
Any complication*	39	4.6	2.08 (1.67–2.56)	<0.0005
2 or more complications	10	6.8	2.57 (1.97–3.36)	<0.0005
3 or more complications	2.0	14.6	5.66 (3.82–8.37)	<0.0005
4 or more complications	0.2	17.4	6.49 (2.20–19.2)	<0.0005

Table 3 Factors associated with patient dissatisfaction and anaesthesia, after adjustment for patient age, sex, ASA status, use of neuromuscular blocking agents and duration of anaesthesia *Complications included sore throat, headache, soft tissue injury, muscle pain, back pain, urinary retention, confusion, neurological deficit, myocardial infarction and renal failure (pain, nausea and vomiting have been excluded)

Variable	Incidence (%)	Adjusted OR (95% CI)	*P*
Any intraoperative adverse event	31	1.12 (0.86–1.46)	0.63
Recovery room			
Any adverse event	70	1.92 (1.47–2.56)	<0.0005
Moderate or severe pain	3.8	6.95 (5.18 –9.33)	<0.0005
Severe nausea or vomiting	0.5	2.85 (1.11–7.34)	0.022
Postoperative review (day after surgery)			
Moderate or severe pain	24	3.94 (3.16–4.91)	<0.0005
Severe nausea or vomiting	9.7	4.09 (3.18–5.25)	<0.0005
Awareness	0.1	54.9 (1507–191)	<0.0005
Any complication*	39	2.04 (1.64–2.56)	<000005
2 or more complications	10	2.41 (1.83–3.16)	<000005
3 or more complications	2.0	5.01 (3.36–7.47)	<0.0005
4 or more complications	0.2	6.25 (2.07–18.9)	0.001

dissatisfied were generally younger (48.5 (19) yr *vs* 54.2 (20) yr) (P<0.0005). They also underwent a shorter duration of anaesthesia (2.18 (1.9) h *vs* 2.43 (2.2) h) (P=0.018). Factors associated with patient dissatisfaction are presented in Table 2. After adjustment for patient and surgical factors, there was a strong relation between patient dissatisfaction and postoperative pain, nausea and vomiting, and other complications (Table 3). Patient medical conditions were no longer associated with patient dissatisfaction after adjustment for perioperative risk (using ASA status).

Discussion

We found a high rate of patient satisfaction with anaesthesia care in patients interviewed on the first day after surgery. Factors most strongly associated with satisfaction included older patient age, male sex and measures of increased perioperative risk (presence of several co-existing medical conditions and ASA status ≥III).

The rate of dissatisfaction was low (3.2%). However, it is recognized that patient responses may be modified to please staff,[2 20] and hence this may be an under-representation of the true level of dissatisfaction. Other hospital satisfaction surveys have reported dissatisfaction rates of less than 15%.[8 14 15] It has been suggested previously that patients do not know what to expect during their hospitalization to allow them to rate their satisfaction appropriately,[8] or only rate selected aspects of their care.[7] We asked patients to rate their satisfaction with anaesthesia care only, at a time when the outcomes from our service were known to them and were fresh in their minds. We did not ask them to rate the entire hospitalization episode for which a variety of other factors may be important.[5–8 14 15 18] Of interest, dissatisfaction with anaesthesia has been reported to be associated with a 12-fold risk of global dissatisfaction with day-case surgery.[15] We did not obtain patient satisfaction data for day-case surgical patients or those unable to cooperate with our survey; our results apply only to patients admitted overnight (at least) after surgery. It is possible that our results were affected by reporting or detection bias in that patients unable to cooperate may have lower satisfaction rates. We believe this is unlikely as these patients were generally older and sicker, and were recovering from more extensive surgery: these factors were associated with improved satisfaction rates in our study. Our survey was performed prospectively using predetermined criteria and asked patients to rate their level of satisfaction, pain control and emesis on graded scales. Our large study population enabled us to identify several important risk factors associated with patient dissatisfaction.

Shorter duration of anaesthesia (a surrogate marker for lesser surgery) and the presence of adverse events in the recovery room and on postoperative review were significantly associated with patient dissatisfaction. These adverse events included moderate or severe pain and severe nausea or vomiting. The risk of dissatisfaction increased as the number of postoperative complications increased. Not surprisingly, we found that awareness, although rare, was strongly associated with patient dissatisfaction. With the exception of awareness, adverse intraoperative events were not related to patient dissatisfaction. This is not surprising given that patients are oblivious to most intraoperative events that do not result in adverse postoperative outcome. Traditionally, the perceived role of the anaesthetist has been restricted to the immediate preoperative and intraoperative periods,[21] whereas anaesthetists are now considered to have greater involvement in preoperative preparation and postoperative care.[22 23] This should allow earlier detection and treatment of postoperative complications.

Patient confidence in the anaesthetist has been reported to be high.[24] Fears of anaesthesia include postoperative nausea and vomiting,[10] prolonged drowsiness[10] and awareness (or not waking up).[25] There has always been a strong focus on anaesthetic morbidity and mortality.[11–13 26 27] These remain important outcomes, yet with improved safety and greater expectations after anaesthesia and surgery, further emphasis should now be placed on other features of postoperative recovery.[23] Quality of recovery[28] and patient satisfaction are two such indices. Methods used to measure patient satisfaction have not been validated extensively in the postoperative population.[6 23] Lee and Lum cautioned against the use of patient satisfaction as a good measure of postoperative outcome.[23] In contrast, Donabedian argued that despite its strengths and limitations, information on patient satisfaction should be indispensable in the assessment of quality in health care.[2] Dexter, Aker and Wright recently developed a valid and reliable measure of patient satisfaction in 86 patients after minor surgical procedures; [29] they also found that unrelieved pain was associated with lower patient satisfaction.

Minor postoperative complications are important to patients and represent an area for potential improvement in anaesthetic, surgical and nursing care. Our study suggests that this may be associated with improved patient satisfaction. It is recognized that women have a greater risk of 'minor' postoperative complications, such as nausea and vomiting, headache and backache,[12 13] and recover less well after operation.[28] Our study confirms these findings and supports greater efforts at preventing or treating such complications (in all patients). Other factors related to improved postoperative recovery and patient satisfaction include individualized preoperative education, adequate communication and interpersonal skills of hospital staff.[7 8 15 25 28] These influences may have changed the patient's overall satisfaction with their hospital stay but were not the subject of this study. It is likely that a patient's participation in a QA survey and the opportunity for anaesthetists to demonstrate their concern for their postoperative well-being adds to patient satisfaction.

Quality in health care is multifaceted.[2 3 30] Its assessment requires multiple measures of process combined with measures of outcome, including patient satisfaction.[2] These aspects should be achievable, despite the current era of cost containment.[31] To our knowledge, this is the largest satisfaction survey of surgical patients published. Our study found that patient satisfaction with anaesthesia was very high and identified several factors associated with dissatisfaction that may be preventable or better treated.

Acknowledgements

We thank all members of the Department of Anaesthesia and Pain Management, and the nursing staff of the operating theatre recovery room for their interest and cooperation with data collection

References

1 Lohr KN, Donaldson MS, Harris-Wehling J. Medicare: a strategy for quality assurance. *Qual Rev Bull* 1992; **18**: 120–6

2 Donabedian A. The quality of care *How can it be assessed? JAMA* 1988; **260**: 1743–8

3 Gill TM, Feinstein AR. A critical appraisal of the quality-of-life measurements. *JAMA* 1994; **272**: 619–26

4 Abbey A, Andrews FM. Modelling the psychosocial determinants of life quality. *Soc Indicators Res* 1985; **16**: 1–34

5 Pascoe G. Patient satisfaction in primary health care. A literature review and analysis. *Evaluation Prog Planning* 1983; **6**: 185–210

6 Westbrook JI. Patient satisfaction. Methodological issues and research findings. *Aust Health Rev* 1993; **16**: 75–88

7 Hall JA, Dornan MC. What patients like about their medical care and how often they are asked. A meta-analysis of the satisfaction literature. *Soc Sci Med* 1988; **27**: 935–9

8 Ward SE, Gordon D. Application of the American Pain Society quality assurance standards. *Pain* 1994; **56**: 299–306

9 Dodds CP, Harding W, Moore DG. Anaesthesia in an Australian private hospital: the consumers' view *Anaesth Intensive Care* 1985; **13**: 325–9

10 Moerman N, van Dam FSAM, Oosting J. Recollections of general anaesthesia: a survey of anaesthesiological practice *Acta Anaesthesiol Scand* 1992; **36**: 767–71

11 Forrest JB, Cahalan MK, Rehder K, *et al.* Multicenter study of general anesthesia. II. Results. *Anesthesiology* 1990; **72**: 262–8

12 Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg* 1994; **78**: 7–16

13 Myles PS, Hunt JO, Moloney JT. Postoperative 'minor' complications. Comparison between men and women. *Anaesthesia* 1997; **52**: 300–6

14 Fitzpatrick R. Surveys of patient satisfaction: II—designing a questionnaire and conducting a survey. *BMJ* 1991; **302**: 1129–32

15 Tong D, Chung F, Wong D. Predictive factors in global and anesthesia satisfaction in ambulatory surgical patients. *Anesthesiology* 1997; **87**: 856–64

16 Osborne GA, Rudkin GE. Outcome after day-care surgery in a major teaching hospital. *Anaesth Intensive Care* 1993; **21**: 822–7

17 O'Connor SJ, Gibberd RW, West P Patient satisfaction with day surgery. *Aust Clin Rev* 1991; **11**: 143–9

18 Harju E. Patient satisfaction among day surgery patients in a central hospital. *Qual Assur Health Care* 1991; **3**: 85–8

19 Pineault R, Contandriopoulos AP, Valois M, *et al* Randomised clinical trial of one day surgery: patient satisfaction, clinical outcomes and costs. *Med Care* 1985; **23**: 171–82

20 Raphael W. Do we know what the patients think? A survey comparing the views of patients, staff and committee members. *Int J Nurs Stud* 1967; 4: 209–23

21 Swinhoe CF, Groves ER. Patients' knowledge of anaesthetic practice and the role of the anaesthetist. *Anaesthesia* 1994; **49**: 165–6

22 Klock PA, Roizen MF. More or better—educating the patient about the anesthesiologist's role as perioperative physician *Anesth Analg* 1996; **83**: 671–2

23 Lee A, Lum ME. Measuring anaesthetic outcomes *Anaesth Intensive care* 1996; **24**: 685–93

24 Shevde K. Panagopoulos G. A survey of 88 patients' knowledge, attitudes and concerns regarding anesthesia. *Anesth Analg* 1991; **73**: 190–8

25 Klafta JM, Roizen MF. Current understanding of patients' attitudes toward and preparation for anesthesia: A review. *Anesth Analg* 1996; **83**: 1314–21

26 Webb RK, Currie M, Morgan C, et *al.* The Australian incident monitoring study: an analysis of 2000 incident reports. *Anaesth Intensive Care* 1993; **21**: 520–8

27 Warden JC, Borton CL, Horan BF. Mortality associated with anaesthesia in New South Wales, 1984–1990. *Med J Aust* 1994; **161**: 585–93

28 Myles PS, Hunt JO, Nightingale CE, *et al.* Development and psychometric testing of a quality of recovery score after general anesthesia in adults. *Anesth Analg* 1999; **88**: 83–90

29 Dexter F, Aker J, Wright WA Development of a measure of patient satisfaction with monitored anesthesia care *Anesthesiology* 1997; **87**. 865–73

30 Maxwell R. Quality assessment in health *BMJ* 1984; **288**: 1470–2

31 Weeks AM, Walsh MK. Fostering progress and development (in an anaesthetic department) at a time of cost containment. *Curr Opin Anesthesiol* 1998; **11**: 217–19

British Journal of Anaesthesia **84** (1): 11–15 (2000)

Validity and reliability of a postoperative quality of recovery score: the QoR-40†

P. S. Myles*, B. Weitkamp, K. Jones, J. Melick and S. Hensen

Department of Anaesthesia and Pain Management, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

**Corresponding author*

Quality of recovery after anaesthesia is an important measure of the early postoperative health status of patients. We attempted to develop a valid, reliable and responsive measure of quality of recovery after anaesthesia and surgery. We studied 160 patients and asked them to rate postoperative recovery using three methods: a 100-mm visual analogue scale (VAS), a nine-item questionnaire and a 50-item questionnaire, the questionnaires were repeated later on the same day. From these results, we developed a 40-item questionnaire as a measure of quality of recovery (QoR-40; maximum score 200). We found good convergent validity between QoR-40 and VAS (r=0.68, P<0.001). Construct validity was supported by a negative correlation with duration of hospital stay (rho=–0.24, P<0.001) and a lower mean QoR-40 score in women (162 (SD 26)) compared with men (173 (17)) (P=0.002). There was also good test–retest reliability (intra-class r_i=0.92, P<0.001), internal consistency (Cronbach's α=0.93, P<0.001) and split-half coefficient (α=0.83, P<0.001). The standardized response mean, a measure of responsiveness, was 0.65. The QoR-40 was completed in less than 6.3 (4.9) min. We believe that the QoR-40 is a good objective measure of quality of recovery after anaesthesia and surgery. It would be a useful end-point in perioperative clinical studies.

Br J Anaesth 2000; **84**: 11–15

Keywords: anaesthesia, audit; measurement techniques, recovery; recovery, postoperative; complications, morbidity; research, anaesthesia; surgery, postoperative period

Accepted for publication: June 30, 1999

Measurement of patient health status, or quality of life, has become an important end-point in clinical studies as it represents, in part, the patient's perception of their outcome of care.[1–4] This approach has rarely been used in anaesthesia and surgery studies[5] which have focused traditionally on other recovery indices, such as time to awakening, duration of stay or various adverse sequelae such as pain, emesis or confusion.[5–10] Although these events are usually transient, they are of major concern to many patients and often leave them with negative recollections of their recovery from surgery.[11–13] Poor quality recovery frequently prolongs duration of stay in the recovery room or delays discharge from hospital, both of which have significant implications for resource utilization.

We have previously developed a nine-item questionnaire to measure quality of recovery after general anaesthesia and surgery.[14] Psychometric evaluation revealed moderate validity and reliability (coefficients 0.50–0.61), suggesting it was an acceptable instrument for *group* measurements. The aim of this study was to develop an expanded questionnaire and test its validity, reliability and responsiveness in hospital surgical practice.

Patients and methods

After obtaining approval from the Ethics Committee and informed consent, we studied male and female patients, aged more than 18 yr, undergoing general anaesthesia and surgery. Patients were excluded if they had poor English comprehension, psychiatric disturbance that precluded complete cooperation, known history of alcohol or drug dependence, or any severe pre-existing medical condition that limited objective assessment after operation.

Baseline (preoperative) data were collected and patients were asked to complete two questionnaires. The first had nine items asking the patient to rate their status on a three point scale, the QoR score.[14] The second was a more comprehensive 50-item questionnaire with items on a five-point Likert scale (for positive items, 1='none of the time' to 5='all of the time'; for negative items the scoring was reversed). (The full questionnaire is available on request from the corresponding author.) The 50 items chosen had been identified previously by patients, their relatives, nursing

---

†The article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

and medical staff as important during the postoperative recovery period.[14] We also collected other perioperative data, such as details of surgery and anaesthesia, duration of stay in the recovery room and total hospital stay.

On the morning after surgery, patients were asked to rate their overall postoperative recovery using a 100-mm visual analogue scale (VAS), marked from 'poor recovery' to 'excellent recovery', as an alternative overall assessment of recovery,[1 14] and then complete the QoR score and 50-item questionnaire. Patients were instructed to record the time taken to complete the 50-item questionnaire and to repeat the QoR score and 50-item questionnaire several hours later (as a measure of repeatability). Inpatients were instructed to place the second set of completed questionnaires in an internal mail envelope. Patients who were discharged home on the day of surgery were given the questionnaires and instructed to complete them the following day, and then return the completed questionnaires in a self-addressed envelope provided.

The 50-item questionnaire was later analysed to remove items that were not correlated with quality of recovery (using the total score), as identified by a Pearson correlation coefficient <0.30. Items removed were: ability to read, hiccups, pain at the needle or i.v. site, cough, leg cramps, dry mouth, constipation, diarrhoea and difficulty with micturition ('trouble with urine'). This resulted in a 40-item questionnaire intended to measure quality of recovery (the QoR-40). The items were then grouped according to various aspects (dimensions) of recovery: emotional state (n=9), physical comfort (n=12), psychological support (n=7), physical independence (n=5) and pain (n=7) (Table 1).

Table 1 Dimensions of the QoR-40 identified to represent aspects of good quality recovery after anaesthesia and surgery. Positive items were scored from 1 (worst) to 5 (best); scores were reversed for negative items. Internal consistency (Cronbach's α) and item-to-own dimension correlation coefficients are presented

	Coefficient
Emotional state (α=0.82)	
Q 2 Feeling comfortable	0.72
Q 9 Having a general feeling of well-being	0.74
Q 12 Feeling in control	0.67
Q.28 Bad dreams	0.45
Q 36 Feeling anxious	0.74
Q.37 Feeling angry	0.63
Q.38 Feeling depressed	0.71
Q.39 Feeling alone	0.66
Q.40 Difficulty falling asleep	0.61
Physical comfort (α=0.83)	
Q.1 Able to breathe easy	0.60
Q.5 Have a good sleep	0.67
Q.10 Being able to enjoy food	0.61
Q.11 Feeling rested	0.59
Q.19 Nausea	0.71
Q.20 Vomiting	0.52
Q.21 Dry retching	0.63
Q.24 Feeling restless	0.65
Q 25 Shaking or twitching	0.48
Q 26 Shivering	0.60
Q 27 Feeling too cold	0.51
Q.34 Feeling dizzy	0.60
Psychological support (α=0.83)	
Q.13 Able to communicate with hospital staff (when in hospital)	0.64
Q.14 Able to communicate with family or friends	0.78
Q.15 Getting support from hospital doctors (when in hospital)	0.67
Q.16 Getting support from hospital nurses (when in hospital)	0.72
Q 17 Having support from family or friends	0.66
Q.18 Able to understand instructions or advice	0.67
Q.35 Feeling confused	0.59
Physical independence (α=0.80)	
Q.3 Able to return to work, or usual home activities	0.67
Q.4 Able to write	0.74
Q 6 Have normal speech	0.52
Q 7 Able to wash, brush teeth or shave	0.85
Q 8 Able to look after own appearance	0.88
Pain (α=0.77)	
Q 22 Moderate pain	0.59
Q.23 Severe pain	0.60
Q 29 Headache	0.60
Q.30 Muscle pains	0.79
Q.31 Backache	0.70
Q.32 Sore throat	0.63
Q.33 Sore mouth	0.69

Validity testing

Validity is a measure of accuracy and was difficult to verify because there were no accepted alternative methods of measuring quality of postoperative recovery (we chose not to use the recently developed QoR score[14] because it had common items and so would have a spuriously high correlation). We used the following to evaluate validity:

(1) Convergent validity: we compared the QoR-40 with the VAS, and also measured inter-item correlations.

(2) Construct validity: we compared the QoR-40 score between men and women, as women were expected to have a poorer quality of recovery on the basis of previous studies.[6–9] We also measured the associations between the QoR-40 and the time required for completion of the questionnaire, duration of stay in the recovery room and duration of hospital stay.

Reliability

Reliability is a measure of consistency and was assessed by:

(1) Test–retest reliability: we asked patients to complete both questionnaires on a second occasion, later on the same postoperative day.

(2) Internal consistency of the QoR-40: we also measured the median correlation between items within each dimension and the item-to-own dimension correlations.

(3) Split-half reliability: we measured the correlation between split segments of the QoR-40.

Clinical acceptability and responsiveness

A health status instrument should be acceptable to patients and staff and be able to detect a meaningful change in health status.[15–17] We used the following:

(1) Recruitment rate.

(2) Time taken for patients to complete the 50-item questionnaire.

(3) Successful completion and return rate.

(4) Responsiveness: we measured standardized response means.[16]

Table 2 Patient characteristics, extent of surgery and timing of assessment (n=160) (mean (SD or range), median [IQR] or number (%))

Age (yr)	44 (18–81)
Sex (M/F) (% male)	75/85 (47)
ASA status (n (%))	
I	71 (44)
II	72 (45)
III	17 (11)
Extent of surgery (n (%))	
Day-case	25 (16)
Minor	78 (49)
Major	57 (36)
Type of surgery (n (%))	
General	48 (30)
Gynaecology	33 (21)
Orthopaedic	25 (16)
Ear, nose and throat	22 (14)
Urology	15 (9)
Other	17 (10)
Duration of surgery (min)	70 [45–120]
Recovery room stay (min)	60 [45–84]

Statistical analysis

Data are presented as mean (SD), median (interquartile range (IQR)) and 95% confidence intervals (95% CI). Associations were measured using Pearson correlation coefficients (r), Spearman rank correlation (rho) or Cronbach's alpha (α); test–retest reliability (concordance) was measured using the intra-class correlation coefficient (r_1).[15] Repeatability was also calculated from the within-subjects SD, based on the Bland–Altman method.[18] Comparisons between correlation coefficients were based on the normal approximation. Changes from baseline were compared using the paired t test. Standardized response means were calculated as the mean change in score divided by its SD.[16] All analyses were performed using SPSS for Windows v8.0 (SPSS Inc., Chicago, IL, USA). The null hypothesis was rejected if two-tailed $P<0.01$.

Results

Of the 192 patients approached in this study, there was only one refusal (recruitment rate >99%); another 26 patients who had been discharged from hospital did not return their questionnaires (completion and return rate 87%). Three patients were excluded; two because their surgical procedure was performed under local anaesthesia and one because of heavy sedation in the intensive care unit. Therefore, there were 160 evaluable patients (age range 18–81 yr) recovering from most types of surgery (Table 2). Neuromuscular blocking agents were used on 111 (69%) occasions. Median hospital duration of stay was 3 (IQR 2–6) days. The questionnaires were completed in hospital by 118 (74%) patients and at home by 42 (26%).

The 50-item questionnaire took 6.3 (4.9) min to complete, and 142 (89%) patients completed it within 10 min. Most patients completed the questionnaire without any assistance, although some required prompting if items were overlooked. Mean preoperative QoR-40 was 183 (SD 17) and after operation, 167 (23). Changes in perioperative health status and responsiveness are summarized in Table 3.

The correlation between the postoperative QoR-40 and VAS was $r=0.68$ ($P<0.0005$). This correlation was consistent for patients recovering from day-case surgery ($r=0.76$), minor surgery ($r=0.66$) and major surgery ($r=0.72$) (all $P<0.0005$). The correlation between the postoperative QoR-40 and VAS was significantly stronger than that between the VAS and QoR score (0.68 *vs* 0.62) ($P<0.0005$).

Men had a higher QoR-40 score than women (173 (17) compared with 162 (26)) ($P=0.002$). There was a significant negative correlation between the QoR-40 and duration of hospital stay (rho=–0.24, $P<0.001$), but not for duration of stay in the recovery room (rho=–0.12, $P=0.11$). There was a negative correlation between the QoR-40 and time required to complete the questionnaire (rho=–0.22, $P<0.001$).

Test–retest reliability and internal consistency for the QoR-40 were high ($r_1=0.92$ and $\alpha=0.93$, respectively) ($P<0.0005$). The split-half coefficient was 0.83 ($P<0.0005$). The test–retest bias was +7.1 and the repeatability coefficient was 24. Test–retest reliability was significantly higher for the QoR-40 than for the QoR score (0.92 *vs* 0.71) ($P<0.0005$).

The median item-to-own dimension coefficients and Cronbach's α for each dimension were: emotional state ($r=0.66$, $\alpha=0.82$), patient comfort ($r=0.63$, $\alpha=0.83$), psychological support ($r=0.67$, $\alpha=0.80$), physical independence ($r=0.74$, $\alpha=0.80$) and pain ($r=0.63$, $\alpha=0.77$). The inter-dimension correlation matrix is shown in Table 4.

Discussion

We have developed and evaluated a 40-item quality of recovery score (QoR-40) in a diverse group of patients recovering from many types of surgery. The validity, reliability and clinical acceptability of the score was excellent, with most patients able to complete the original 50-item questionnaire in less than 10 min.

Because there is no gold standard measurement of good quality postoperative recovery, we chose to validate the QoR-40 using a variety of end-points. Content validity has been demonstrated previously.[14] The evidence of construct validity was strong, with the QoR-40 being able to discriminate between men and women; it is known that women generally have a worse postoperative recovery.[6–9] We were able to demonstrate a negative association between the QoR score and duration of hospital stay. The finding that inter-dimension correlations were moderate, and that each dimension was better correlated with the overall QoR-40, supports construct validity. Reliability was also confirmed. The reliability coefficients of the QoR-40 exceeded published recommendations (>0.70 to 0.80),[4 17] indicating that the QoR-40 should provide reliable assessment for both group and individual measurements and/or comparisons.

We derived five clinically relevant dimensions which

Table 3 Change in health status of patients interviewed before operation (preoperative baseline) and again on the day after surgery (postoperative) (mean (SD)). The QoR score is a nine-item score[14] and the QoR-40 is a 40-item score consisting of five dimensions. Standardized response mean=mean change in score divided by its SD

Score	**Maximum possible score**	**Preoperative**	**Postoperative**	**Mean change (95% CI)**	**% Change from baseline**	**Standardized response mean**
QoR score	18	16.2 (1.9)	13.8 (3.3)	−2.4 (−3.0 to −1.8)	15%	0.73
QoR-40 dimensions						
Emotional state	45	41.6 (9.0)	38.1 (6.0)	−3.5 (−5.3 to −1.7)	8%	0.35
Physical comfort	60	55.4 (9.9)	48.7 (8.5)	−6.8 (−8.7 to −4.8)	13%	0.80
Psychological support	35	34.8 (6.9)	33.1 (3.2)	−1.7 (−3.0 to −0.4)	5%	0.24
Physical independence	25	23.6 (2.5)	18.8 (5.1)	−4.8 (−5.9 to −3.9)	20%	0.91
Pain	35	31.9 (3.9)	28.8 (5.4)	−3.1 (−4.0 to −2.1)	10%	0.59
Global QoR-40	200	181 (17)	167 (23)	−16 (−20 to −11)	9%	0.65

Table 4 Inter-dimension correlations for the QoR-40 (inter-dimension $\alpha=0.85$). Each dimension consists of a number of items (as indicated in parentheses)

	QoR-40	**1**	**2**	**3**	**4**	**5**
QoR-40 dimensions						
(1) Emotional state (*n*=9)	0.90	–				
(2) Physical comfort (*n*=12)	0.90	0.79	–			
(3) Psychological support (*n*=7)	0.69	0.57	0.50	–		
(4) Physical independence (*n*=5)	0.69	0.48	0.49	0.44	–	
(5) Pain (*n*=7)	0.81	0.70	0.64	0.47	0.43	–

encompass most aspects of good quality postoperative recovery. Each was internally consistent and correlated well with the global QoR-40. Our psychometric evaluation would support combining of scores into a single index, as has been suggested previously.[1] Gill and Feinstein also suggested 10 criteria by which to judge health status measurements;[1] the QoR-40 can satisfy all of these. Other methods have been recommended when describing the ability of a health status instrument to detect a clinically important treatment effect or responsiveness.[15–17] We calculated standardized response mean values of 0.24–0.91, suggesting a strong ability to detect a clinically important change in quality of recovery, even for small numbers of patients.[16] As might be expected, pain, physical comfort and physical independence were most affected by surgery and anaesthesia in our study. Although dimension scores for emotional state and psychological support decreased after surgery, they were probably already compromised before operation and should be less prone to change if hospital staff are attentive to patients' psychological wellbeing throughout the perioperative period. It is likely that scores would have been lower if patients were interviewed at an earlier time after surgery (most would have already recovered significantly from anaesthesia), and this would have detected greater changes in health status and responsiveness.

Similarly, some of the validity and reliability coefficients may be underestimates in view of the nature of our study population. Many of our patients were anxious before operation and some were medically unstable or in pain; these circumstances probably did not provide an ideal baseline for comparison: a QoR-40 measurement after complete recovery may have achieved higher estimates. The test–retest coefficient is also likely to be an underestimate in view of the general ongoing improvement in patients' health status after operation. This contention is supported by the positive test–retest bias.

Patient priorities may differ from those of anaesthetists and surgeons. Postoperative recovery has traditionally been evaluated using a variety of physical, psychological and economic end-points.[5–10] In some circumstances it may be more relevant to measure patients' quality of recovery[14] or their satisfaction with care.[5 12 13] Emphasis on quality becomes more important given the safety of modern anaesthesia.[6 7 9] If most patients can be anaesthetized safely and recover after surgery, then efforts should be made to improve their quality of recovery. Any dimension of the QoR-40 can be targeted at specific assessment if a patient rates it as particularly important to them.[1 2] For example, a patient may wish to regain their usual physical functioning as soon as possible or avoid all pain and physical discomfort, whereas another may require specific emotional and psychological support. With increased interest in quality of care, contemporary hospital practice focuses more strongly on individual patient requirements and thus should place greater emphasis on patient-rated assessment of care.

We have reported previously the validity and reliability of a shorter nine-item instrument, the QoR score.[14] Our present study has confirmed its psychometric properties and demonstrated its responsiveness, but we also found that the QoR-40 had superior validity and reliability. The QoR-40, with its relevant dimensions, should also be more discriminative. This suggests that the QoR score should be reserved for conditions where a simple, rapid evaluation is required (such as audit or other quality assurance activity). The QoR-40 provides a more extensive, yet efficient evaluation of a patient's quality of recovery after anaesthesia and surgery. The QoR-40 would be a useful outcome measure in perioperative clinical studies and for assessing the impact of changes in health care delivery on quality of care.

Acknowledgement

Earlier work, which formed the basis of this study, was funded by a research grant from the Australian and New Zealand College of Anaesthetists.

References

1 Gill TM, Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. *JAMA* 1994, **272**: 619–26

2 Guyatt GH, Cook DJ. Health status, quality of life, and the individual *JAMA* 1994; **272**: 630–1

3 Editorial. Quality of life and clinical trials. *Lancet* 1995; **346**: 1–2

4 McDowell I, Newell C *Measuring Health: a Guide to Rating Scales and Questionnaires*. New York: Oxford University Press, 1987

5 Lee A, Lum ME. Measuring anaesthetic outcomes. *Anaesth Intensive Care* 1996; **24**· 685–93

6 Cohen MM, Duncan DG, Pope WDB, Wolkenstein C. A survey of 112,000 anaesthetics at one teaching hospital (1975–1983). *Can J Anaesth* 1987; **33**: 22–31

7 Forrest JB, Cahalan MK, Rehder K, *et al.* Multicenter study of general anesthesia. II. Results. *Anesthesiology* 1990; **72**: 262–8

8 Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting *Anesth Analg* 1994; **78** 7–16

9 Myles PS, Hunt JO, Moloney JT. Postoperative 'minor' complications: comparison between men and women. *Anaesthesia* 1997; **52**: 300–6

10 Warden JC, Borton CL, Horan BF. Mortality associated with anaesthesia in New South Wales, 1984–1990. *Med J Aust* 1994, **161**: 585–93

11 Moerman N, van Dam FSAM, Oosting J. Recollections of general anaesthesia: a survey of anaesthesiological practice. *Acta Anaesthesiol Scand* 1992; **36**· 767–71

12 Tong D, Chung F, Wong D. Predictive factors in global and anesthesia satisfaction in ambulatory surgical patients *Anesthesiology* 1997, **87**: 856–64

13 Dexter F, Aker J, Wright WA Development of a measure of patient satisfaction with monitored anesthesia care *Anesthesiology* 1997; **87**. 865–73

14 Myles PS, Hunt JO, Nightingale CE, *et al* Development and psychometric testing of a quality of recovery score after general anesthesia and surgery in adults *Anesth Analg* 1999; **88** 83–90

15 Guyatt G, Walter S, Norman G. Measuring change over time· assessing the usefulness of evaluative instruments. *J Chronic Dis* 1987; **40**: 171–8

16 Katz JN, Larson MG, Phillips CB, Fossell AH, Liang MH Comparative measurement sensitivity of short and longer health status instruments. *Med Care* 1992; **30**: 917–25

17 Kirshner B, Guyatt G. A methodological framework for assessing health indices. *J Chronic Dis* 1985; **38**: 27–36

18 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986, **i**. 307–10

British Journal of Anaesthesia 84 (1): 16–22 (2000)

Aprotinin does not impair renal haemodynamics and function after cardiac surgery†

A. Schweizer[1], L. Höhn[1], D. R. Morel[2], A. Kalangos[3] and M. Licker[1]*

[1]Division of Anaesthesiology, [2]Division of Anaesthesiological Investigations and [3]Clinics of Cardiovascular Surgery, Hôpital Cantonal Universitaire, CH-1211 Geneve 14, Switzerland

**Corresponding author*

Patients undergoing cardiac surgery with moderate hypothermic cardiopulmonary bypass (CPB) were allocated randomly to receive either saline (control group, n=29) or a high-dose regimen of aprotinin (aprotinin group, n=28). In both groups, CPB was associated with similar and transient increases in effective renal plasma flow (+54% in controls and +48% in aprotinin-treated patients) and in fractional excretion of sodium and potassium, but glomerular filtration rate remained unchanged. Plasma and urinary ratios of 6-keto-PGF$_{1\alpha}$ to thromboxane B$_2$ (TxB$_2$) increased significantly, indicating systemic and renal release of vasodilatory prostaglandins. Osmolar clearance correlated with urinary excretion of cyclic GMP (r=0.79 and 0.86 in the control and aprotinin groups, respectively) and 6-keto-PGF$_{1\alpha}$ (r=0.63 and 0.69 in the control and aprotinin groups, respectively). Compared with preoperative values, plasma atrial natriuretic peptide increased after weaning from CPB (+71% and +93% in the control and aprotinin groups, respectively). Aprotinin had no apparent adverse effect on renal function and it did not alter mechanisms involving prostanoids and atrial natriuretic peptide during cardiac surgery.

Br J Anaesth 2000; **84**: 16–22

Keywords: polypeptides, aprotinin; surgery, cardiovascular; kidney, function; kidney, blood flow; hormones, prostaglandins; kidney, atrial natriuretic factor

Accepted for publication: August 2, 1999

Aprotinin, a non-specific serine protease inhibitor extracted from bovine lung or porcine gut, can reduce bleeding and blood transfusion requirements in patients undergoing cardiac operations, liver transplantation and orthopaedic surgery.[1-3] The use of aprotinin has become widespread and is not limited to patients at increased risk of bleeding or those undergoing complex surgical procedures.[4]

However, concerns have been raised regarding its possible effects on renal function: in pigs, a large dose of aprotinin caused a reduction in renal blood flow during acute stress[5] and a multicentre, randomized, controlled study[6] reported more frequent increases in serum creatinine (>0.5 mg dl^{-1}) in patients given aprotinin compared with placebo (30% *vs* 8%, respectively). Aprotinin is a small molecule (6512 Da) and is freely filtered by the glomeruli and nearly completely absorbed. Some suggest that the breakdown capacities of the convoluted tubules could be overwhelmed, allowing nephrotoxic effects.[7] In addition, aprotinin inhibits kallikrein, the key enzyme in the kinin-generating pathway, which triggers the release of potent vasodilatory mediators, such as prostacyclin and nitric oxide, from endothelial and renal tubular cells.[8 9] In contrast, aprotinin delays degradation of atrial natriuretic peptide (ANP),[10] and greater plasma concentrations of ANP may counteract inhibition of the kallikrein–kinin system in the kidney and promote diuresis and renal vasodilatation.

We designed a randomized double-blind study to assess the effects of aprotinin on renal haemodynamics and function in patients undergoing cardiac surgery. In addition, we questioned if release of vasoconstrictor and vasodilatory prostanoids (thromboxane A$_2$ (TxA$_2$) and prostacyclin) and plasma ANP and cyclic GMP (cGMP), its second messenger, were influenced by aprotinin pretreatment.

Patients and methods

After obtaining Institutional Ethics Committee approval and informed consent, we studied 60 patients undergoing elective coronary artery bypass graft surgery, aortic valve replacement and mitral valve replacement or repair. We excluded those with diabetes or creatinine clearance values less than 30 ml min^{-1}. Patients in whom postoperative bleeding needed surgical haemostasis were also excluded.

The patient's usual cardiac medications were administered up to the morning of surgery. Peripheral venous, radial arterial and central venous catheters were inserted for

---

†This article is accompanied by Editorial II.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

fluid and drug administration in addition to haemodynamic measurements. Before operation, crystalloid 10 ml kg^{-1} was infused over 20 min. General anaesthesia was standardized using fentanyl 40–60 µg kg^{-1} and midazolam 0.03–0.06 mg kg^{-1} followed by pancuronium 0.10 mg kg^{-1} h^{-1} for neuromuscular block (0.15 mg kg^{-1} at induction and 0.05 mg kg^{-1} during bypass). Mechanical ventilation was adjusted to obtain normocapnia and normoxia.

Before cannulation of the aorta and right atrium, heparin sodium 300 u kg^{-1} was administered; additional heparin was given if the kaolin-activated clotting time (Hemochron 401, International Technidyne Corporation, Edison, NJ, USA) was less than 550 s. Non-pulsatile cardiopulmonary bypass (CPB) was started with a membrane oxygenator (Cobe Laboratories Inc., Lakewood, CO, USA) primed with crystalloid 2 litre; body temperature was decreased to achieve moderate hypothermia (26–30°C) with α-stat regulation for pH management. After aortic clamping, myocardial protection was provided with St Thomas's solution 600–900 ml infused through the aortic root and repeated at 25–30-min intervals. During CPB, mean arterial pressure was maintained at 55–70 mm Hg using sodium nitroprusside, phenylephrine, or both. Pump flow was maintained at greater than 2 and 2.4 litre min^{-1} m^{-2} during hypothermia and rewarming, respectively. After completion of the distal vascular anastomosis or valve surgery, patients were weaned from CPB when rectal temperature was at least 35.5°C.

Fluids and vasoactive and inotropic agents were given to optimize haemodynamic conditions; packed red blood cells were given if blood haemoglobin concentration was less than 9 g dl^{-1}.

Study procedure

Patients were allocated randomly to one of two treatment groups in a double-blind manner. Each patient received a similar volume of saline or aprotinin. In the aprotinin group, each patient received 2 million kallikrein inhibitory units (mkiu) over 30 min, 1 mkiu in the CPB priming volume and 0.5 mkiu h^{-1} i.v. from the start of surgery until skin closure. The mean dose was 4.1 mkiu/patient or approximately 50 000 kiu kg^{-1}.

Before anaesthesia, priming doses of inulin 30 mg kg^{-1} (10% Inulin; Laevosan Gesellschaft mbH, Linz, Austria) and p-paraimmunohippurate 8 mg kg^{-1} (PAH, Merck, Sharp and Dohme, NJ, USA) were given i.v. followed by a continuous infusion of both drugs at 0.2 and 0.15 mg kg^{-1} min^{-1}, respectively, up to the end of surgery. An equilibration period of 60 min was allowed before baseline measurements. Diuretics, mannitol or dopamine were not given during the study.

Kallikrein concentrations were measured in urinary samples before and after bypass using the method of Amundsen and colleagues.[11] This assay measured urinary activity against the chromogenic substrate S-2266 (H-D-Val-Leu-Arg-pNA, AB Kabi Diagnostica, Stockholm, Sweden) for which urine kallikrein is highly specific. Results are expressed as nkat $litre^{-1}$, where 1 nkat is the amount of glandular kallikrein which cleaves 0.05 mmol of substrate per minute. Intra- and inter-assay coefficients of variation were 4.2% and 7.1%, respectively.

Measurements and calculations

Mean arterial pressure, heart rate and right atrial pressure were recorded. Glomerular filtration rate was assumed to equal creatinine or inulin clearances (C_{IN}, C_{creat}) and effective renal plasma flow was estimated as PAH clearance (C_{PAH}) Other tests of renal function included osmolar clearance (C_{Osm}), water clearance (C_{H_2O}) and fractional sodium and potassium excretion. Blood and urinary samples were obtained at the following times: (1) baseline measurement, 30 min before induction of anaesthesia (preop.), (2) before the start of bypass (pre-bypass), (3) before the second cardioplegia (bypass), (4) after administration of protamine (post-bypass) and (5) on day 5 after operation. During operation, urine was collected over 30 min and arterial blood was obtained in the middle of each sampling period. Before and after operation, urine was collected over 12 h and mean blood concentrations (for creatinine and electrolytes) at the beginning and end of the clearance period were calculated Arterial blood was collected into cold tubes containing indomethacin and heparin (for prostaglandin assay) or dipotassium ethylenediamino-tetraacetic acid and aprotinin (for ANP and cGMP assay) and was centrifuged immediately at 4°C. C_{IN} and C_{PAH} were measured only during operation. Urinary and plasma inulin and PAH concentrations were assayed spectrophotometrically. Serum and urinary sodium and creatinine were measured with a standard flame emission photometer. All clearance values were corrected for a standard body surface area of 1.73 m^2.

Plasma concentrations of ANP and its second messenger cGMP, in addition to plasma and urinary concentrations of the stable metabolites of TxA_2 (thromboxane B_2 (TxB_2)) and prostacyclin (6-keto-$PGF_{1\alpha}$) were determined before anaesthesia and during operation (pre-op., pre-bypass, bypass and post-bypass). Plasma ANP was extracted from a 2-ml plasma aliquot on a C-18 octadecylsilane cartridge (Sep-Pak, Waters Associates, Milfford, MA, USA) and measured by a specific radioimmunoassay; intra- and inter-assay variations were 3.9% and 13.7%, respectively. cGMP was measured after extraction by ethanol using a commercial kit (Amersham, UK); intra- and inter-assay variations were 4.5% and 10%, respectively.

TxB_2 and 6-keto-$PGF_{1\alpha}$ concentrations were measured in 100-µl aliquots of plasma or urine by radioimmunoassay without extraction (Amersham, UK). The lower limit of sensitivity was 30 pg ml^{-1} for both measurements. Excretion of urinary prostanoid metabolites was expressed as pg g $creatinine^{-1}$.

Plasma concentrations of ANP, cGMP and prostanoids were corrected for the haemodiluting effects of CPB according to the change in packed cell volume.

Intra- and postoperative i.v. fluid requirements (packed red blood cells, fresh frozen plasma, crystalloid and colloid

Table 1 Clinical and surgical data (mean (range) or number of patients) No significant differences between groups

	Control group (n=29)	**Aprotinin group (n=28)**
Patient characteristics		
Age (yr)	64 (33–81)	66 (35–85)
Sex (M/F)	21/8	21/7
Body surface (m^2)	1.8 (1.5–2.1)	1.9 (1.6–2.2)
Left ventricular ejection fraction (%)	61 (35–80)	62 (40–75)
Serum creatinine (mg dl^{-1})	98 (66–151)	103 (61–210)
Preoperative treatment		
Nitrates (n)	17	13
β-blockers (n)	9	8
Calcium channel blockers (n)	8	9
Angiotensin converting-enzyme inhibitors (n)	10	7
Salicylates (n)	23	18
Heparin (n)	5	1
Surgical procedure		
CABG (n)	19	17
Valvular surgery (n)	7	6
Combined (n)	3	5
Aortic clamping (min)	90 (52–171)	107 (39–245)
CPB duration (min)	145 (73–297)	152 (61–290)
Pharmacological support after CPB		
Dobutamine (n)	7	9
Epinephrine or norepinephrine (n)	8	6

solutions) were recorded for each patient. Postoperative blood loss was measured and recorded by observing the volume of drainage into volumetric chest tube drains until their removal (approximately 24–36 h).

Statistical analysis

Sample size calculation was based on estimates of urinary excretion of cGMP and prostanoids, determined in a preliminary experiment. The calculations indicated that 28 patients were needed in each group to show a difference of ≥1.2 SD (power=90%, significance=5%).

All data are expressed as mean (SD or range); differences were considered significant if $P<0.05$. Two-way analysis of variance with Dunnett's test was used for within-group comparisons with respect to baseline. Chi-square analysis with Yates' correction was used to compare percentages of patients. Simple linear correlation (Pearson) or regression analysis was used to evaluate the relationship between variables. For ANP, cGMP and prostanoid analysis, data were log transformed and the concentration equal to the sensitivity of the assay was assigned the value of the statistical limit of significance.

Results

Patient characteristics and outcome

We studied 57 patients (29 in the control group and 28 in the aprotinin group); one patient in each group was subsequently excluded because of bleeding which required re-operation. Another patient in the aprotinin group had a massive myocardial infarct and died shortly after surgery.

Patient characteristics, preoperative treatment and surgical data did not differ between groups (Table 1). There were similar changes in mean arterial pressure, heart rate and right atrial pressure in the two groups (data not shown). Temporary inotropic and/or vasopressor support was needed for weaning from CPB in 14 patients in the saline group and in 15 in the aprotinin group; intra-aortic counterpulsation was required in one patient in each group. Postoperative myocardial infarct was diagnosed in two patients in the saline and in one patient in the aprotinin group. Duration of mechanical ventilation, stay in the ICU and time to discharge did not differ between groups.

In the aprotinin group, postoperative blood loss (775 (314) ml) and blood transfusion requirements (1.4 (0.7) u) were significantly less than in the control group (1185 (403) ml and 2.6 (1.4) u, respectively).

Perioperative renal function

In the control group, urinary kallikrein excretion did not change from before to after bypass (2.52 (1.94) and 3.14 (2.18) kat $litre^{-1}$, respectively) whereas aprotinin treatment was associated with significant lower urinary kallikrein excretion (0.24 (0.22) and 0.31 (0.30) kat $litre^{-1}$, respectively).

Renal function did not differ between groups at any time (Table 2). CPB was associated with significant increases in urinary flow, C_{Osm} and fractional excretion of sodium and potassium; all of these variables were still significantly increased shortly after weaning from CPB and had recovered to preoperative values by day 5 after operation. During CPB, C_{PAH} increased in the control and aprotinin groups (+54% and +48%, respectively). C_{creat} and C_{IN} did not change significantly throughout the study and were correlated with each other ($r=0.72$, $P<0.05$).

Plasma ANP, plasma and urinary cGMP

There were no differences between groups in plasma concentrations of ANP or plasma and urinary values of cGMP. In all

Table 2 Renal function data for patients undergoing cardiac surgery (mean (SD)).*$P<0.05$ compared with preoperative values, no significant difference between groups

	Preoperative	**Intraoperative**			**Day 5 after operation**
		Pre-bypass	**Bypass**	**Post-bypass**	
Urinary flow (ml min^{-1})					
Control group	1.1 (0.4)	1.3 (0.9)	6.1 (3.7)*	3.5 (2.6)*	1.3 (0.4)
Aprotinin group	0.9 (0.4)	1.9 (1.1)	5.2 (3.0)*	4.6 (2.9)*	1.2 (0.5)
Creatinine clearance (ml min^{-1} 1.73 m^{-2})					
Control group	77 (22)	88 (41)	83 (36)	86 (38)	82 (28)
Aprotinin group	74 (29)	90 (39)	93 (48)	82 (32)	74 (25)
Inulin clearance (ml min^{-1} 1.73 m^{-2})					
Control group	–	61 (22)	65 (19)	72 (29)	–
Aprotinin group	–	56 (23)	73 (25)	68 (27)	–
PAH clearance (ml min^{-1} 1.73 m^{-2})					
Control group	–	261 (93)	412 (161)*	396 (155)*	–
Aprotinin group	–	259 (108)	389 (151)*	373 (135)*	–
Osmolar clearance (ml min^{-1} 1.73 m^{-2})					
Control group	1.7 (0.6)	2.0 (1.0)	6.6 (4.2)*	4.0 (3.2)*	1.6 (0.5)
Aprotinin group	1.6 (0.5)	2.7 (1.3)	6.7 (3.7)*	6.0 (3.5)*	1.7 (0.5)
Water clearance (ml min^{-1} 1.73 m^{-2})					
Control group	–0.6 (0.6)	–0.8 (0.7)	–0.5 (0.9)	–0.5 (0.9)	–0.4 (0.6)
Aprotinin group	–0.8 (0.5)	–0.7 (1.1)	–0.9 (1.1)	–0.6 (1.0)	–0.5 (0.4)
Fractional excretion of Na$^+$ (%)					
Control group	0.8 (0.3)	1.1 (0.5)	7.1 (3.8)*	3.8 (2.6)*	1.2 (0.7)
Aprotinin group	0.9 (0.4)	1.0 (0.5)	6.6 (3.6)*	4.5 (2.9)*	1.1 (0.6)
Fractional excretion of K$^+$ (%)					
Control group	12.3 (2.9)	14.7 (3.2)	28.1 (10.1)*	36.1 (16.6)*	8.2 (4.5)
Aprotinin group	13.6 (4.5)	14.5 (4.6)	30.7 (13.2)*	35.2 (17.3)*	9.7 (4.7)

patients, plasma ANP decreased during bypass and increased after weaning from bypass (+71% in the control group and +93% in the aprotinin group), compared with preoperative baseline values (Fig. 1). There was a significant correlation between plasma ANP and plasma cGMP (r=0.52 in controls and r=0.62 in the aprotinin group) and between plasma ANP and right atrial pressure (r=0.41 in controls and r=0.52 in the aprotinin group).

Changes in plasma cGMP mimicked those of plasma ANP, although they did not reach statistical significance. Urinary excretion of cGMP increased significantly during and after bypass and was positively correlated with C_{Osm} (r=0.79 and 0.86 in the control and aprotinin groups, respectively).

Plasma and urinary TxB_2 and 6-keto-$PGF_{1\alpha}$

Patients in the aprotinin group did not differ from those in the control group in plasma concentrations and urinary excretion of 6-keto-$PGF_{1\alpha}$ and TxB_2 and their respective ratios. After the start of bypass, the ratio of plasma concentrations of 6-keto-$PGF_{1\alpha}$ to TxB_2 increased significantly because of an increase in 6-keto-$PGF_{1\alpha}$, while TxB_2 remained unchanged (Fig. 2).

Urinary excretion of TxB_2 and 6-keto-$PGF_{1\alpha}$ increased significantly during and after CPB. The ratio of 6-keto-$PGF_{1\alpha}$ to TxB_2 was increased because of greater urinary excretion of 6-keto-$PGF_{1\alpha}$ than TxB_2 (Fig. 3). In the two groups, C_{Osm} was directly related to urinary excretion of 6-keto-$PGF_{1\alpha}$ (r= 0.63 and 0.69 in the control and aprotinin groups) and to the ratio of 6-keto-$PGF_{1\alpha}$ to TxB_2 (r=0.52 and 0.54 in the control and aprotinin groups, respectively).

Discussion

As acute renal failure is related to mortality in cardiac surgery, clinicians should be aware of the potential renal damage from drugs. In this regard, we found that in patients with good renal function, aprotinin treatment (with a mean dose of 4.1 mkiu) did not affect renal function during cardiac surgery with moderate hypothermic CPB. CPB impaired renal solute reabsorption, regardless of aprotinin pretreatment, and was associated with renal release of vasodilatory mediators (nitric oxide and prostacyclin), indicated by urinary excretion of their respective metabolites (cGMP and 6-keto-$PGF_{1\alpha}$).

Aprotinin dose regimen

Different doses of aprotinin have different effects on coagulation, fibrinolysis and the inflammatory cascade.[12] Compared with the standard high-dose aprotinin treatment (2 mkiu before bypass, 2 mkiu in the pump prime and an infusion of 0.5 mkiu h^{-1}), a smaller dose (using only 2 mkiu in the pump prime) can also reduce postoperative blood loss.[13 14] At plasma concentrations greater than 50 kiu ml^{-1}, plasmin is inhibited, whereas 200 kiu ml^{-1} is needed to suppress plasma kallikrein. According to a pharmacokinetic model proposed by Levy, Bailey and Salmenpera,[15] target plasma concentrations of 200 kiu ml^{-1} can be achieved with a bolus of aprotinin 2 mkiu in the pre-bypass period, 1 mkiu added to the CPB circuit and an infusion of 0.5 mkiu h^{-1}. We used a slightly higher dose regimen (1 mkiu instead of 0.5 mkiu in the pump prime) that gave a 34% reduction in postoperative blood loss and

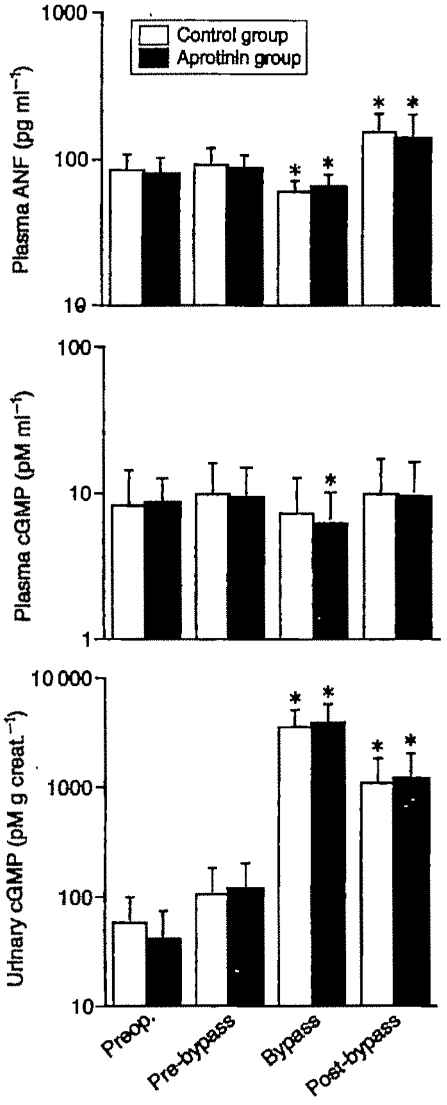


Fig 1 Changes in plasma atrial natriuretic peptide (ANP) and plasma and urinary cyclic guanidine monophosphate (cGMP) in the two groups of patients undergoing cardiac surgery. Data are mean (SD) *Significant difference from baseline (preoperative) ($P<0.05$). No differences between groups.

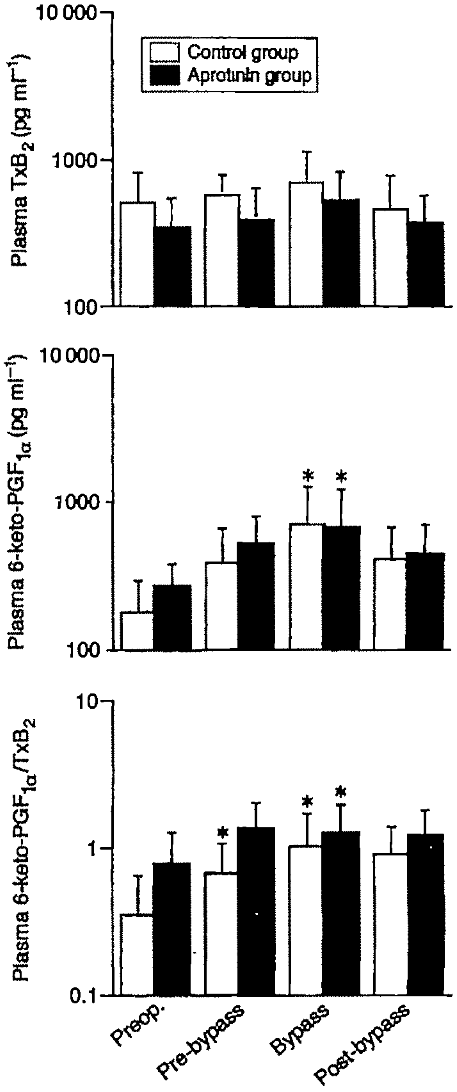


Fig 2 Changes in plasma thromboxane B_2 (TxB_2) and 6-keto-$PGF_{1\alpha}$, and the ratio 6-keto-$PGF_{1\alpha}$ to TxB_2 in the two groups of patients undergoing cardiac surgery Data are mean (SD) *Significant difference from baseline (preoperative) ($P<0.05$).

reduced allogenic blood transfusion. As the affinity of aprotinin for renal tissue is greater than for plasma kallikrein, it was not surprising to observe 90% suppression of urinary excretion of kallikrein.

Aprotinin and ANP–cGMP and prostanoids pathways

Plasma concentrations of ANP and systemic and renal formation of TxA_2, prostacyclin and nitric oxide were similar in the two groups. The relationships we found between plasma concentrations of ANP, plasma cGMP and right atrial pressure confirmed that, even during operation, atrial release of ANP is triggered by changes in cardiac filling pressure[16 17] and that plasma ANP concentrations largely determine circulating concentrations of its second messenger cGMP.[18] Although we observed no change in plasma concentrations of ANP after infusion of aprotinin, we cannot exclude the possibility that inhibition of ANP metabolism[10] was compensated for by a reduction in ANP synthesis in atrial tissues.

Increased plasma and urinary ratios of 6-keto-$PGF_{1\alpha}$ to TxB_2 during CPB indicate that the balance of prostanoid synthesis was shifted towards prostacyclin-induced vasodilatation which could prevent the vasoconstrictive and thrombogenic effect of TxA_2.

In clinically relevant concentrations (50–500 mkiu), aprotinin had no effect on endothelial and tubular release of prostacyclin[19] and therefore it did not influence perioperative plasma and urinary 6-keto-$PGF_{1\alpha}$ concentrations.

In contrast with previous reports showing reduced platelet release of TxA_2 in aprotinin-treated patients, we found similar plasma TxB_2 concentrations in the two groups.[20 21]

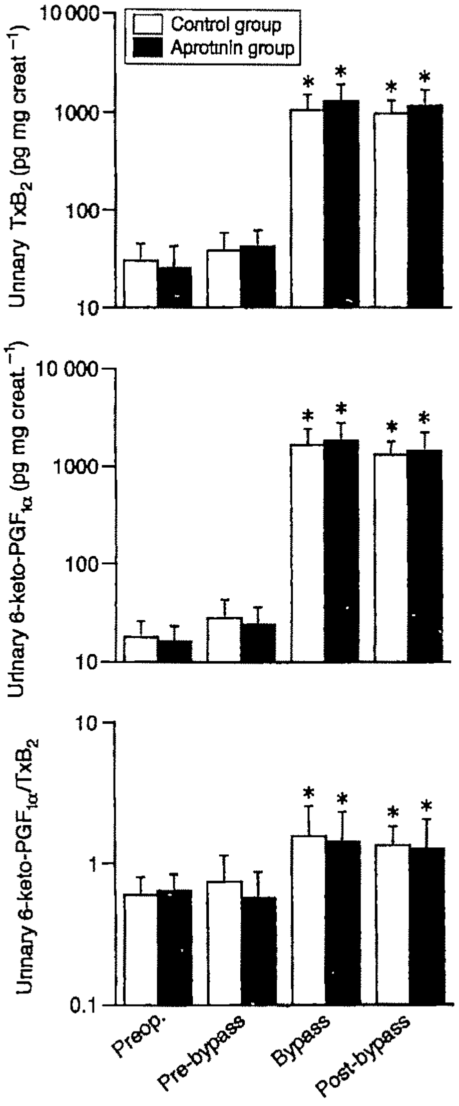


Fig 3 Changes in urinary excretion of thromboxane B_2 (TxB_2) and 6-keto-$PGF_{1\alpha}$, and the urinary ratio 6-keto-$PGF_{1\alpha}$ to TxB_2 in the two groups of patients undergoing cardiac surgery. Data are mean (SD) *Significant difference from baseline (preoperative) ($P<0.05$).

In fact, maximal release of PGI_2 occurs shortly after the start of CPB whereas peak plasma TxB_2 concentrations occur during rewarming at the end of CPB.[22] As we measured prostaglandins approximately 20 min after the start of CPB and before chest closure, we were unable to document the suppressive effect of aprotinin on plasma TxB_2.

Renal dysfunction and CPB

As reported elsewhere,[23] we found no reduction in glomerular filtration rate and renal plasma flow during hypothermic extracorporeal bypass as long as mean arterial pressure and pump flow were maintained within the physiological range of autoregulation. In the two groups, increased C_{PAH} overestimated renal plasma flow because tubular extraction of PAH was reduced. Transient tubular dysfunction was characterized by impaired solute reabsorption, a brisk osmolar diuresis and increases in fractional excretion of sodium and potassium. Importantly, we observed a close relationship between osmolar diuresis and renal production of vasodilatory mediators during cardiac surgery. Urinary excretion of 6-keto-$PGF_{1\alpha}$, TxB_2 and cGMP reflect renal synthesis of prostacyclin, TxA_2 and nitric oxide[24] During hypothermic CPB, enhanced salt and water excretion may result from several mechanisms: first, prostanoids antagonize the *in vivo* effect of antidiuretic hormone and inhibit Na^+/Cl^- reabsorption in the proximal and distal nephron and in the loop of Henle[25]; second, in the papilla, PGI_2- and NO-mediated medullary vasodilatation prevents the papillary Na^+/Cl^- countercurrent exchange by disrupting the hyperosmolar gradient[26]; third, tubular solute reabsorption is impaired by reduced activity of Na^+/Cl^- membrane pumps during hypothermia.

Aprotinin, cardiac surgery and renal dysfunction

The use of aprotinin in clinical practice has not been associated with an increased incidence of postoperative renal failure.[27–29] In patients undergoing deep hypothermic arrest, the benefits and safety of aprotinin need further study.[30 31] In a large multicentre study,[32] the need for haemodialysis or filtration was strongly related to poor preoperative renal function, vascular disease and heart failure, type of surgery and use of intra-aortic balloon pump

Despite inhibition of the kallikrein–kinin pathways, aprotinin pretreatment did not influence prostaglandin synthesis, glomerular filtration, renal plasma flow or tubular transport mechanisms. This suggests that the kallikrein–kinin pathways play a minor role in renal homeostasis and that other factors (e.g. renin–angiotensin system) may stimulate the synthesis of prostanoids during cardiac surgery. Interestingly, in animal models of sepsis[33] and in humans with cirrhosis,[34] aprotinin can reverse systemic vasodilatatory hypotension and improve renal function.

In contrast with our data and other studies,[27 28 35] some investigators reported mild and transient postoperative increases in serum creatinine concentrations, C_{Osm} and FE_{Na+} in patients given aprotinin.[6 20] However, these studies were not designed to assess renal outcome, changes in renal function were not great and no details were available on perioperative haemodynamic control and the use of fluids, diuretics and mannitol. For instance, in the study of Blauhut and colleagues,[20] increased C_{Osm} was more likely related to significant higher arterial pressure values which resulted in pressure-induced natriuresis in aprotinin-treated patients.

In summary, we found no evidence that in patients undergoing cardiac surgery with hypothermic bypass, a high dose of aprotinin had an adverse effect on renal function or influenced its autoregulatory control mechanisms involving prostanoids and ANP. Nevertheless, until more data are available, a lower dose is still recommended in patients who have diabetes mellitus or renal insufficiency, and in those receiving chronic treatment with angiotensin-converting inhibitors or undergoing deep hypothermic CPB.[36]

References

1 Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). *J Thorac Cardiovasc Surg* 1989; **97**: 364–72

2 Scudamore CH, Randall TE, Jewesson PJ, *et al*. Aprotinin reduces the need for blood products during liver transplantation. *Am J Surg* 1995; **169**: 546–9

3 Janssens M, Joris J, David JL, Lemaire R, Lamy M. High-dose aprotinin reduces blood loss in patients undergoing total hip replacement surgery. *Anesthesiology* 1994, **80**: 23–9

4 Fremes SE, Wong BI, Lee E, *et al*. Metaanalysis of prophylactic drug treatment in the prevention of postoperative bleeding. *Ann Thorac Surg* 1994; **58**: 1580–8

5 Maier M, Starlinger M, Zhegu Z, Rana H, Binder BR. Effect of the protease inhibitor aprotinin on renal hemodynamics in the pig. *Hypertension* 1985; **7**: 32–8

6 D'Ambra MN, Akins CW, Blackstone EH, *et al*. Aprotinin in primary valve replacement and reconstruction. a multicenter, double-blind, placebo-controlled trial. *J Thorac Cardiovasc Surg* 1996; **112**· 1081–9

7 Werle E, Trautschold I, Haendle H, Fritz H. Physiologic, pharmacologic, and clinical aspects of proteinase inhibitors. *Ann NY Acad Sci* 1968; **146**: 464–78

8 Regoli D, Barabe J. Pharmacology of bradykinin and related kinins. *Pharmacol Rev* 1980; **32**: 1–46

9 Proud D, Kaplan AP. Kinin formation: mechanisms and role in inflammatory disorders. *Annu Rev Immunol* 1988; **6**: 49–83

10 Vanneste Y, Pauwels S, Lambotte L, Michel A, Dimaline R, Deschodt-Lanckman M. Respective roles of kallikrein and endopeptidase 24.11 in the metabolic pathway of atrial natriuretic peptide in the rat. *Biochem J* 1990; **269**: 801–6

11 Amundsen E, Putter J, Friberger P, Knos M, Larstraten M, Claeson G. Methods for the determination of glandular kallikrein by means of chromogenic tri-peptide substrate. *Adv Exp Med Biol* 1979; **120A**: 83–95

12 Fritz H, Fink E, Truscheit E. Kallikrein inhibitors. *Fed Proc* 1979; **38**: 2753–9

13 Laupacis A, Fergusson D. Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome. The International Study of Peri-operative Transfusion (ISPOT) Investigators. *Anesth Analg* 1997; **85**. 1258–67

14 Davis R, Whittington R. Aprotinin: a review of its pharmacology and therapeutic efficacy in reducing blood loss associated with cardiac surgery. *Drugs* 1995; **49**: 954–83

15 Levy JH, Bailey JM, Salmenpera M. Pharmacokinetics of aprotinin in preoperative cardiac surgical patients. *Anesthesiology* 1994; **80**: 1013–18

16 Raine AE, Erne P, Burgisser E, *et al*. Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. *N Engl J Med* 1986, **315**. 533–7

17 Schaff HV, Mashburn JP, McCarthy PM, Torres EJ, Burnett JC. Natriuresis during and early after cardiopulmonary bypass: relationship to atrial natriuretic factor, aldosterone and antidiuretic hormone. *J Thorac Cardiovasc Surg* 1989; **98**: 979–86

18 Dussaule J-C, Vahanian A, Michel P-L, *et al*. Plasma atrial natriuretic factor and cyclic GMP in mitral stenosis treated with balloon valvulotomy. *Circulation* 1988; **78**: 276–85

19 Royston BD, Royston D, Coade SB, Morgan DM, Pearson JD. Aprotinin does not inhibit the release of prostacyclin or von Willebrandt factor from cultured human endothelial cells. *Thromb Haemost* 1992; **67**: 172–5

20 Blauhut B, Gross C, Necek S, Doran JE, Spath P, Lundsgaard-Hansen P. Effects of high-dose aprotinin on blood loss, platelet function, fibrinolysis, complement, and renal function after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1991; **101**: 958–67

21 Nagaoka H, Innami R, Murayama F, *et al*. Effects of aprotinin on prostaglandin metabolism and platelet function in open heart surgery. *J Cardiovasc Surg* 1991; **32**: 31–7

22 Faymonville M-E, Deby-Dupont G, Larbuisson R, *et al*. Prostaglandin E2, prostacyclin, and thromboxane changes during nonpulsatile cardiopulmonary bypass in humans. *J Thorac Cardiovasc Surg* 1986; **91**· 858–66

23 Andersson LG, Jepson A, Bratteby LE, *et al* Renal function during cardiopulmonary bypass· influence of the calcium entry blocker felopidine. *Anesth Analg* 1996; **83**: 34–40

24 Frolich JC, Wilson TW, Sweetman BJ, *et al*. Urinary prostaglandins: identification and origin. *J Clin Invest* 1975; **55**: 763–70

25 Agnoli GC, Borgatti R, Cacciari M, Ikonomu E, Lenzi P, Marinelli M. Effective role of the renin–angiotensin system in the control of prostanoid synthesis and renal function in healthy women with moderate salt depletion. *Clin Physiol* 1996; **16**: 41–59

26 Parekh N, Zou A-P. Role of prostaglandins in renal medullary circulation: response to different vasoconstrictors. *Am J Physiol* 1996; **40**. F653–8

27 Lemmer JH Jr, Stanford W, Bonney SL, *et al*. Aprotinin for coronary artery bypass grafting: effect on postoperative renal function. *Ann Thorac Surg* 1995; **59**: 132–6

28 Dietrich W, Barankay A, Hahnel C, Richter JA High-dose aprotinin in cardiac surgery: three years' experience in 1,784 patients. *J Cardiothorac Vascular Anesth* 1992; **6**: 324–7

29 Bidstrup BP, Harrison J, Royston D, Taylor KM, Treasure T. Aprotinin therapy in cardiac operations: a report on use in 41 cardiac centers in the United Kingdom. *Ann Thorac Surg* 1993; **55**: 971–6

30 Okita Y, Takamoto S, Ando M, Morota T, Yamaki F, Kawashima Y. Is use of aprotinin safe with deep hypothermic circulatory arrest in aortic surgery? Investigations on blood coagulation. *Circulation* 1996; **94**: 177–81

31 Parolari A, Antona C, Alamanni F, *et al*. Aprotinin and deep hypothermic circulatory arrest: there are no benefits even when appropriate amounts of heparin are given. *Eur J Cardiothorac Surg* 1997; **11**: 149–56

32 Chertow GM, Lazarus JM, Christiansen CL, *et al* Preoperative renal risk stratification. *Circulation* 1997; **95**: 878–84

33 Cumming AD, Nimmo GR. Hemodynamic, renal, and hormonal actions of aprotinin in an ovine model of septic shock. *Crit Care Med* 1992; **20**: 1134–9

34 MacGilchrist A, Craig KJ, Hayes PC, Cumming AD. Effect of the serine protease inhibitor, aprotinin, on systemic haemodynamics and renal function in patients with hepatic cirrhosis and ascites. *Clin Sci* 1994; **87**: 329–35

35 Levy JH, Pifarre R, Schaff HV, *et al*. A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. *Circulation* 1995; **92**. 2236–44

36 Dobkowski WB, Murkin JM. A risk–benefit assessment of aprotinin in cardiac surgical procedures. *Drug Safety* 1998; **18**· 21–41

British Journal of Anaesthesia 84 (1): 23–7 (2000)

A placebo-controlled study of the effects of dopexamine on gastric mucosal perfusion in infants undergoing hypothermic cardiopulmonary bypass

P. D. Booker[1]* and M. Pozzi[2]

[1]*University of Liverpool, Royal Liverpool Children's Hospital, Eaton Road, Liverpool L12 2AP, UK.*
[2]*Royal Liverpool Children's Hospital, Eaton Road, Liverpool L12 2AP, UK*
**Corresponding author*

We used a laser Doppler probe to measure gastric mucosal blood flow (flux) and a paediatric tonometer to intermittently calculate gastric–arterial P_{CO_2} difference (Pr_{CO_2}–Pa_{CO_2} gap) in 50 infants aged 0.3–52 weeks who required hypothermic cardiopulmonary bypass (CPB). During CPB, patients in group 2 (n=25) were given dopexamine 1.0 mg kg^{-1} over 5 min, followed by an infusion of 2 µg kg^{-1} min^{-1}. Patients in group 1 (n=25) received an equal volume of saline. Drug allocation was random and blinded. Measurements of flux, Pr_{CO_2}–Pa_{CO_2} gap and mean femoral arterial pressure (MAP) were made over 5 min during steady state before and after cooling on CPB to 18–24°C. MAP and blood lactate concentrations were similar in both groups throughout CPB. Mean flux decreased from 182 (SD 60) at the beginning of CPB to 158 (51) after rewarming on CPB in group 1, whereas it increased from 180 (56) to 196 (49) in group 2. This post-rewarm flux was significantly greater in group 2 than in group 1 (P= 0.01). Similarly, mean Pr_{CO_2}–Pa_{CO_2} gap increased significantly from 3.6 (6.3) to 8.2 (6.7) in group 1 (P=0.01) compared with a significant decrease from 5.8 (5.5) to 2.1 (5.5) in group 2 (P=0.02). Mean Pr_{CO_2}–Pa_{CO_2} gap after rewarming in group 2 was significantly higher than that in group 1 (P=0.001). These data indicate that dopexamine may be useful in maintaining normal gut perfusion in infants requiring hypothermic CPB.

Br J Anaesth 2000; **84**: 23–7

Keywords: heart, cardiopulmonary bypass; sympathetic nervous system, dopexamine; gastrointestinal tract, mucosal perfusion; neonates; infants; measurement techniques, flowmetry

Accepted for publication: July 30, 1999

Our previous studies showed that transient gut mucosal ischaemia may occur in infants during and after cardiopulmonary bypass (CPB).[1–3] Severe decreases in mucosal perfusion may be a causative factor in postoperative necrotizing enterocolitis[4–6] or multiple organ dysfunction (MOF).[7 8] In previous studies, we demonstrated that neonates with aortic arch anomalies[2] and infants subjected to CPB-induced profound hypothermia[1] may be at particular risk of developing splanchnic ischaemia in the perioperative period. CPB, even at a flow rate equivalent to a normal cardiac output, can reduce delivery of oxygen to the tissues by haemodilution,[9 10] microvessel occlusion secondary to platelet or erythrocyte aggregation,[11] and high blood concentrations of vasoconstrictor hormones such as angiotensin II,[12] vasopressin,[13] thromboxane,[14] endothelin-1[15] and catecholamines.[16] Moreover, CPB flow rates are frequently reduced to a fraction of normal cardiac output, using profound hypothermia to reduce cellular oxygen requirements.

Dopaminergic receptors have been identified in human intestinal villus and mucosal arterioles[17] and increases in gastric mucosal blood flow, as measured using laser Doppler flowmetry (LDF), follow injection of dopamine into the gastric submucosa.[18] A study in adults undergoing CPB showed that dopamine may increase gastric mucosal blood flow, as measured using LDF, by more than 85%.[19] In contrast, however, adult patients with sepsis had a 28% decrease in mucosal blood flow after dopamine.[20] Similarly, animal work suggests that low-dose dopamine may exacerbate gut ischaemia[21] or reduce mucosal blood flow, despite increasing superior mesenteric arterial flow.[22] Dopexamine has shown more consistent promise as a splanchnic vasodilator in experimental[23–25] and clinical studies.[26 27] In dogs, dopexamine is less potent than dopamine at dopaminergic (DA_1 and DA_2) receptors but is a much more potent β_2-adrenergic receptor agonist.[28] Although agonist activity at either of these receptor subtypes decreases mesenteric arterial vascular resistance, β_2-adrenergic receptor stimula-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

tion may be more effective.[29] However, although some clinical studies in critically ill adults that compared the effects of dopamine and dopexamine on gut mucosal perfusion showed dopexamine to be superior,[27 30] other studies showed no significant difference between the two drugs.[31] Moreover, it is probable that dopaminergic receptors undergo variable postnatal maturation,[32] making extrapolation of data from adults to infants somewhat questionable.

There have been very few paediatric studies of the haemodynamic effects of dopexamine. One short-term clinical study in children with sepsis suggested that dopexamine 0.5–1 μg kg^{-1} min^{-1} significantly improved splanchnic perfusion.[33] However, a study in preterm neonates confirmed that dopexamine 2 μg kg^{-1} min^{-1} increased global perfusion and arterial pressure[34] and hence any beneficial effects that dopexamine may have on regional vascular perfusion may be secondary to an increase in cardiac output. Even in more sophisticated adult studies it has been difficult to differentiate the specific regional vascular effects of dopexamine from its direct and indirect effects on cardiac output.[26 35] CPB offers a useful physiological model to help clarify whether or not dopexamine can affect regional perfusion while cardiac output is kept constant. We demonstrated previously in an unblinded pilot study that dopexamine increased mucosal perfusion in infants undergoing CPB, and hence we wished to confirm these preliminary findings in a blinded, randomized, controlled study.

Patients and methods

With Local Ethics Committee approval and written informed parental consent, we studied 50 infants, >3.0 kg in weight, aged 0.3–52 weeks, requiring >60 min elective hypothermic CPB. Patients requiring inotropic drugs before operation and those with aortic arch anomalies were excluded.

No premedication was given. Anaesthesia was induced with thiopental 4 mg kg^{-1} and neuromuscular block was achieved with vecuronium 0.2 mg kg^{-1} h^{-1}. Anaesthesia was maintained with 0.5% isoflurane in oxygen and/or air before and after CPB, supplemented with alfentanil 10 μg kg^{-1} i.v. followed by an infusion of 2 μg kg^{-1} min^{-1}. Midazolam 0.2 mg kg^{-1} was added to the pump prime blood. Routine monitoring included insertion of a cannula into the femoral artery for measurement of systemic arterial pressure. A paediatric TRIP tonometry catheter 8F (Datex-Ohmeda Ltd) was inserted via the mouth into the patient's stomach and connected to a Tonocap monitor (Datex-Ohmeda Ltd) which intermittently analysed $P\mathrm{CO}_2$ in the tonometer balloon (Pr_{CO_2}). The monitor was calibrated previously in accordance with the manufacturer's recommendations using a special gas mixture containing 5% carbon dioxide. Each measurement of Pr_{CO_2} was combined with a measurement of Pa_{CO_2}, temperature corrected,[36] to allow calculation of the Pr_{CO_2}–Pa_{CO_2} gap.

Correct positioning of the tonometer was aided by the sight of a small bulging of the anterior abdominal wall as the catheter was advanced gently. In addition, after routine probe calibration, a laser Doppler probe (Moor Instruments Ltd) was slid into the lumen of a size 8-FG nasogastric tube and inserted into the stomach using the same technique as for the tonometry catheter. Positioning of the probe against the stomach wall was confirmed when the probe was connected to the MBF3 monitor (Moor Instruments Ltd) and computer by observing typical pulse synchronous oscillation.[19] Later analysis of recordings was made using Moorsoft data interpretation software (Moor Instruments Ltd).

After sternotomy, but before surgical manipulation of the great vessels, baseline recordings of gastric mucosal flux, Pr_{CO_2} and femoral mean arterial pressure (MAP) were made over a 5-min period (pre-CPB). A sample of arterial blood was obtained for measurement of blood-gas values and blood lactate concentrations. The hollow fibre D701 oxygenator (Dideco) used for CPB was primed with warmed blood and crystalloid such that blood and core temperatures after initiation of CPB were approximately 34±0.5°C and packed cell volume (PCV) was 25–30%. When the patient had been started on non-pulsatile CPB at a flow rate of 100 ml kg^{-1} min^{-1} for 10 min and nasopharyngeal temperature remained constant to within ±0.1°C, MAP, Pr_{CO_2} and flux values were recorded for another 5 min (W1.CPB). Another arterial blood sample was obtained for measurement of PCV, blood-gas values and lactate concentrations.

Patients were allocated randomly to one of two groups to receive either 0.9% saline (group 1) or dopexamine diluted in 0.9% saline (group 2), using a random figure table and sealed envelope system. An assistant, not otherwise involved in the study, prepared the drug syringes so that blinding of the observer was maintained. Immediately after the first set of readings during CPB had been obtained, patients in group 2 received dopexamine 1.0 mg kg^{-1} over 5 min, followed by an infusion of 2 μg kg^{-1} min^{-1}. The control group received an equivalent infusion of saline. All infusions were given into a central vein. Patients were perfusion-cooled to 18–24°C, depending on the anticipated duration of low flow required. The rate of cooling and rewarming was controlled to approximately 1°C min^{-1}. PCV was maintained at 25–30% throughout CPB by addition of blood or colloid as necessary. We ensured that mixed venous saturation was maintained >70% and Pa_{O_2} kept at 10–20 kPa (depending on the pre-CPB Pa_{O_2}) using in-line electrodes (Polystan UK, Ltd). A capnograph (Datex Ohmeda Ltd), attached to the gas outlet port of the oxygenator, helped maintain a constant Pa_{CO_2} (5.3±0.5 kPa, temperature uncorrected). When the patient was rewarmed on CPB to 34°C, and nasopharyngeal temperature and MAP had not changed significantly over a 5-min period, another set of blood-gas values, MAP, flux and Pr_{CO_2} readings were obtained over 5 min (W2.CPB). When these rewarm readings were complete, the dopexamine/saline infusion was stopped, the heart was allowed to eject and patients

Table 1 Patient details and measurements obtained before cardiopulmonary bypass (CPB) Normally distributed data are presented as mean (SD) and non-parametric data as median [interquartile range]. Pr_{CO_2}–Pa_{CO_2} gap=difference between P_{CO_2} of gas in tonometer balloon and Pa_{CO_2}, MAP=mean femoral arterial pressure No significant differences between groups

	Group 1 (*n*=25)	**Group 2 (*n*=25)**
Age (weeks)	18.4 [13.3]	25.3 [17.4]
Weight (kg)	4.7 [1.4]	5.4 [4.0]
No of cyanotic patients (%)	32	40
Duration of CPB (min)	106 [44]	118 [108]
Aortic clamp time (min)	47 [23]	54 [28]
Flux (arbitrary units)	254 (82)	242 (62)
(Pr_{CO_2}–Pa_{CO_2}) gap (mm Hg)	−0.9 (4.3)	0.7 (4.4)
MAP (mm Hg)	50.3 (8.4)	48.4 (10.4)
Lactate concn (mmol litre^{-1})	1.3 (0.3)	1.2 (0.4)

Table 2 Mean (SD) gastric mucosal flux, gastric Pr_{CO_2}–Pa_{CO_2} gap, mean femoral arterial pressure (MAP) and blood lactate concentrations in the two groups of patients at steady state after initiation of cardiopulmonary bypass (W1 CPB) and at steady state after rewarming to 34°C on CPB (W2 CPB) Patients in group 2 received a loading dose of dopexamine 1 mg kg^{-1} after the initial CPB readings had been obtained, followed by an infusion of 2 μg kg^{-1} min^{-1} throughout CPB Patients in group 1 were given an equivalent volume of saline. $^{**}P=0.01$, $^{***}P=0.001$ between groups

	Group 1 (*n*=25)	**Group 2 (*n*=25)**
W1.CPB flux (arbitrary units)	182 (60)	180 (56)
W1 CPB (Pr_{CO_2}–Pa_{CO_2}) gap (mm Hg)	3.6 (6.3)	5.8 (5.5)
W1 CPB MAP (mm Hg)	36 (13)	34 (10)
W1 CPB lactate concn (mmol litre^{-1})	3.9 (0.9)	3.8 (1.0)
W2 CPB flux (arbitrary units)	158 (51)	196 (49)**
W2 CPB (Pr_{CO_2}–Pa_{CO_2}) gap (mm Hg)	8.2 (6.7)	2.1 (5.5)**
W2 CPB MAP (mmHg)	43 (8.1)	46 (5.2)
W2 CPB lactate concn (mmol litre^{-1})	5.2 (2.6)	4.5 (2.0)
ΔFlux (W1 CPB flux–W2 CPB flux)	24 (46)	−19 (37)***

were given inotropic support as required to aid weaning from CPB.

Our previous studies indicated that it is during rewarming that mucosal hypoxia is most likely to occur, and as 'flux' is an arbitrary unit of measurement, the change in flux (Δflux) from the first CPB reading (W1.CPB) to that recorded after rewarming (W2.CPB) was used as our primary outcome measure. Data from our preliminary unblinded pilot study were used to calculate the number of patients required in the study. Using a sample size of 25 for each group, we calculated that the study would have a power of more than 90% to yield a statistically significant result. This computation assumed that the mean difference in Δflux between groups would be at least 40 and the common within-group SD would be 40. This effect was selected as the smallest effect that would be clinically significant and that could be reasonably anticipated. Study data have not invalidated these assumptions. We confirmed that our flux and Pr_{CO_2} data were normally distributed using normal probability plots (SPSS v.9.0, SPSS UK Ltd). We used a two-sample *t* test to compare inter-group perfusion data and a paired *t* test to compare intra-group perfusion data. Normally distributed data are presented as mean (SD) and non-parametric data, such as weight and CPB time, are presented as median (interquartile range).

Results

Patients in group 1 were slightly younger and had slightly shorter operations than those in group 2, although these differences were not statistically significant. Eight patients in group 1 and 10 in group 2 were cyanosed before CPB, either because of tetralogy of Fallot or transposition of the great arteries. Most other patients had atrioventricular septal defects. Our measurements obtained both before and after initiation of CPB confirmed that the two groups were comparable in global indices of perfusion (MAP and blood lactate concentrations) and regional indices of perfusion (flux and Pr_{CO_2}–Pa_{CO_2} gap) (Tables 1, 2).

MAP measured at the initial CPB study period (W1.CPB) was significantly lower than that measured after rewarming to 34°C (W2.CPB) in both groups (P=0.03). Lactate concentrations increased in both groups, although this was significant only for group 1 (P=0.01). However, there were significant differences between the two groups in flux and intramucosal pH (pHi) (Table 2). In group 1, mean mucosal flux at W1 CPB was 182 (60) which decreased to 158 (51) after rewarming (W2.CPB) (P=0.02). In contrast, mean flux increased slightly from 180 (56) at W1.CPB to 196 (49) at W2.CPB in group 2 (ns). The gastric Pr_{CO_2}–Pa_{CO_2} gap increased from 3.6 (6.3) to 8.2 (6.7) in group 1 (P=0.01) whereas it decreased slightly in group 2 from 5.8 (5.5) at W1.CPB to 2.1 (5.5) at W2.CPB (ns).

Discussion

We have shown that dopexamine increased gastric mucosal perfusion in infants after rewarming from profound hypothermia, with a significant increase in flux and a decrease in Pr_{CO_2}–Pa_{CO_2} gap that were not seen in the control group. We are unaware of any comparable studies of the effects of dopexamine on splanchnic perfusion in infants or children undergoing cardiac surgery. Clinical studies involving adults undergoing normothermic cardiopulmonary bypass were unable to demonstrate a significant effect of dopexamine on pHi during surgery.[35 37] However, hepatic venous saturation did not change in these patients, suggesting adequate splanchnic oxygenation despite the decrease in pHi,[35] which may have reflected a change in arterial pH and Pa_{CO_2} rather than signifying mucosal ischaemia.[37] In contrast, it has been shown in adults that dopamine can significantly increase gastric mucosal blood flow, as measured by laser Doppler flowmetry, during constant flow CPB at 34°C.[19] The methods of our study are not directly comparable with any of these adult studies, however, as our patients were rewarmed from profound hypothermia and after significant reductions in CPB flow rate. We have shown previously that these conditions consistently produce significant changes in flux and pHi.[1 3 12] We believe, therefore, that our study is more likely to demonstrate drug-induced changes in gastric mucosal perfusion than studies in adult patients subjected to constant flow at normothermia. Although determination of optimum drug dose during CPB is problematic, the method has the particular advantage of allowing measurement of drug-induced changes in regional perfusion, without permitting any confounding effects of drug-induced changes in cardiac output.

It is common practice in most cardiac centres to continually monitor mixed venous saturation, mean arterial pressure and Pa_{O_2} during CPB, together with intermittent measurement of blood-gas values and blood lactate concentrations. However, although these variables may be a useful guide to the adequacy of global oxygen delivery, they cannot exclude inadequate regional perfusion.[38 39] Experimental and clinical studies suggest that if pHi decreases or the Pr_{CO_2}–Pa_{CO_2} gap increases while global indices of perfusion remain normal, mucosal hypoxia is a likely cause.[40–42] Theoretical[43] and clinical[44] evidence suggests that the Pr_{CO_2}–Pa_{CO_2} gap may be a more specific and reliable index of gastric mucosal oxygenation than pHi. Nevertheless, measurement of the Pr_{CO_2}–Pa_{CO_2} gap provides only an indirect assessment of the adequacy of gastric mucosal perfusion. When blood flow to the mucosa decreases, the Pr_{CO_2}–Pa_{CO_2} gap remains small until oxygen delivery becomes barely adequate to maintain normal tissue aerobic metabolism. It is only when blood flow decreases further that the Pr_{CO_2}–Pa_{CO_2} gap increases. Hence any direct relationship between the Pr_{CO_2}–Pa_{CO_2} gap and more direct measures of mucosal blood flow such as flux occur only at relatively low levels of mucosal perfusion.[40] Measurements of gastric mucosal flux represent a real-time measure of blood flow, but in a small volume of tissue. The method involves shining a weak laser light out of a special probe and measuring the Doppler frequency shift in the reflected light induced by moving red blood cells. The limitations and inherent assumptions required by both of these methods of assessing gut mucosal perfusion have been discussed previously.[1 3 12 45] We believe they are sufficiently robust to draw the conclusion that the prevention and treatment of gut mucosal hypoxia in infants undergoing CPB is not only worthwhile but achievable. The consistent and divergent direction of change in both flux and Pr_{CO_2}–Pa_{CO_2} gap induced by dopexamine contrasts strikingly with the changes seen in the control group, despite similar values for global perfusion indices in the two groups.

The dose of dopexamine in our study was the same as that used in one neonatal trial[34] but was twice as high as that used in children with sepsis.[33] We deliberately chose a relatively high dose. The CPB circuit priming volume increased the total volume of circulating blood by at least 200% for all patients. We used a loading dose of dopexamine and a high rate infusion continuing for at least 45 min in all patients so that we could be confident that blood concentrations of dopexamine were high enough to produce a therapeutic effect. Moreover, as dopexamine has no α-adrenergic agonist effects,[28] use of a high-dose regimen during CPB ensures maximum dopaminergic and β_2-adrenergic receptor agonism, with little danger of unwanted vasoconstriction. Although dopexamine is a weak inhibitor of neuronal catecholamine uptake, experimental studies suggest that any potential for vasoconstriction as a result of an increased blood concentration of norepinephrine is far outweighed by a dose-dependent increase in β_2-adrenergic receptor agonism.[28] Relatively stable MAP readings throughout CPB in the dopexamine group support this hypothesis. Dopexamine, at an infusion rate of 2 μg kg^{-1} min^{-1}, inconsistently increases heart rate in adults,[46 47] but this chronotropic effect is less obvious in neonates.[34] Similarly, although we observed that mean heart rate in group 2 was higher than that in group 1 during rewarming, this difference was not clinically or statistically significant.

Further studies to define the optimum dose, duration of infusion and potential for adverse events should be performed before more general use of dopexamine in the perioperative period can be recommended for this age group. Furthermore, most infants undergoing profound hypothermia under CPB do not suffer from postoperative problems that can be related to gut mucosal hypoxia in the peroperative period. Hence routine use of dopexamine during CPB is unjustified. However, our data suggest that infants with aortic arch anomalies, who are at particular risk of gut mucosal hypoxia, may benefit from administration of dopexamine during CPB. Study of this particular subgroup of patients may need a multicentre approach.

Acknowledgements

Financial support for the study was given by the Royal Liverpool Children's Hospital Research Fund.

References

1 Booker PD, Prosser DP, Franks R. Effect of hypothermia on rectal mucosal perfusion in infants undergoing cardiopulmonary bypass. *Br J Anaesth* 1996; **77**: 591–6

2 Booker PD, Romer H, Franks R. Gut mucosal perfusion in neonates undergoing cardiopulmonary bypass. *Br J Anaesth* 1996; **77**: 597–602

3 Booker PD, Davis AJM, Franks R. Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril. *Br J Anaesth* 1997, **79**: 14–18

4 Silane MF. Symchych PS. Necrotizing enterocolitis after cardiac surgery. A local ischemic lesion? *Am J Surg* 1977; **133**: 373–6

5 Kleinman PK, Winchester P, Brill PW. Necrotizing enterocolitis after open heart surgery employing hypothermia and cardiopulmonary bypass. *AJR* 1976; **127**: 757–60

6 Hebra A, Brown MF, Hirschl RB. Mesenteric ischemia in hypoplastic left heart syndrome. *J Pediatr Surg* 1993; **28**: 606–11

7 Biffl WL, Moore EE. Splanchnic ischaemia/reperfusion and multiple organ failure. *Br J Anaesth* 1996; **77**: 59–70

8 Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of postoperative organ dysfunction. *Intensive Care Med* 1994; **20**: 203–9

9 Crystal GJ, Rooney MW, Salem MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. *Anesth Analg* 1988; **67**: 211–18

10 Kiel JW, Riedel GL, Shepherd AP. Effects of hemodilution on gastric and intestinal oxygenation. *Am J Physiol* 1989; **256**: H171–8

11 Boros M, Takaichi S, Hatanaka K. Ischemic time-dependent microvascular changes and reperfusion injury in the rat small intestine. *J Surg Res* 1995; **59**. 311–20

12 Booker PD, Davis AJM, Diver MJ. Angiotensin II concentrations and gut mucosal perfusion in infants undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1999; **13**: 446–50

13 Lehot JJ, Villard J, Piriz H. et *al.* Hemodynamic and hormonal responses to hypothermic and normothermic cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1992; **6**: 132–9

14 Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 1992, **54**: 1236–43

15 Hashimoto K, Miyamoto H, Suzuki K, et *al.* Evidence of organ damage after cardiopulmonary bypass. The role of elastase and vasoactive mediators. *J Thorac Cardiovasc Surg* 1992; **104**: 666–73

16 Reves JG, Karp RB, Buttner EE, et *al.* Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. *Circulation* 1986; **66**: 49–55

17 Amenta F, Collier WL, Ricci A Autoradiographic localization of vascular dopamine receptors. *Am J Hypertension* 1990; **3**. 34–6S

18 Kaise M, Echizen H, Ishizaki T. Dopaminergic control of gastric mucosal blood flow in humans. *Dig Dis Sci* 1993; **38**: 1169–74

19 Karzai W, Gunnicker M, Scharbert G, et *al.* Effects of dopamine on oxygen consumption and gastric mucosal blood flow during cardiopulmonary bypass in humans. *Br J Anaesth* 1996, **77**: 603–6

20 Nevière R, Mathieu D, Chagnon JL, et *al.* The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med* 1996, **154**: 1684–8

21 Segal JM, Phang PT, Walley KR. Low-dose dopamine hastens onset of gut ischaemia in a porcine model of haemorrhagic shock. *J Appl Physiol* 1992; **73**: 1159–64

22 Giraud GD, MacCannell KL. Decreased nutrient blood flow during dopamine- and epinephrine-induced intestinal vasodilation. *J Pharmacol Exp Ther* 1984; **230**: 214–20

23 Cain SM, Curtis SE. Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. *Crit Care Med* 1991; **19**: 1552–60

24 Schmidt H, Secchi A, Wellman R, et *al.* Dopexamine maintains intestinal villus blood flow during endotoxemia in rats. *Crit Care Med* 1996, **24**: 1233–7

25 Bastien O, Piriou V, Aouifi A, et *al.* Effects of dopexamine on blood flow in multiple splanchnic sites measured by laser Doppler velocimetry in rabbits undergoing cardiopulmonary bypass. *Br J Anaesth* 1999; **82**: 104–9

26 Smithies MN, Yee TH, Jackson L, et *al.* Protecting the gut and the liver in the critically ill. effects of dopexamine. *Crit Care Med* 1994; **22**: 789–95

27 Maynard ND, Bihari DJ, Dalton RN, et *al.* Increasing splanchnic blood flow in the critically ill. *Chest* 1995; **108**: 1648–54

28 Smith GW, O'Connor SE. An introduction to the pharmacological properties of Dopacard (dopexamine hydrochloride) *Am J Cardiol* 1988; **62**: 8–17C

29 Braatvedt GD, Flynn MD, Stanners A, et *al.* Splanchnic blood flow in man. evidence for mediation via a β-adrenergic mechanism. *Clin Sci* 1993; **84**: 201–7

30 Sinclair DG, Houldsworth PE, Keogh B, et *al* Gastrointestinal permeability following cardiopulmonary bypass· a randomized study comparing the effects of dopamine and dopexamine. *Intensive Care Med* 1997; **23**: 510–16

31 Bellamy MC, Young Y, Guillou PJ, et *al.* Effects of dopamine and dopexamine on splanchnic microcirculation during major surgery in humans *Br J Anaesth* 1996, **76**: 587P

32 Felder RA, Felder CC, Eisner GM, et *al.* The dopamine receptor in adult and maturing kidney *Am J Physiol* 1989; **257** F315–27

33 Murdock IA, Morrison GC, Dalton NR, et *al* Low dose dopexamine improves indices of hepato-splanchnic perfusion in children recovering from sepsis. *Intensive Care Med* 1996; **22**: S71

34 Kawczynski P, Piotrowski A. Circulatory and diuretic effects of dopexamine infusion in low-birth-weight infants with respiratory failure. *Intensive Care Med* 1996; **22**: 65–70

35 Berendes E, Mollhoff T, Van Aken H, et *al.* Effects of dopexamine on creatinine clearance, systemic inflammation, and splanchnic oxygenation in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1997; **84**: 950–7

36 Chapman MV, Woolf RL, Mythen MG. Temperature dependent errors using gastrointestinal tonometry: an in vivo study. *Br J Anaesth* 1999; **82**: A580

37 Gardeback M, Settergren G. Dopexamine and dopamine in the prevention of low gastric mucosal pH following cardiopulmonary bypass. *Acta Anaesthesiol Scand* 1995; **39**: 1066–70

38 McDaniel LB, Zwischenberger JB, Vertrees RA, et *al.* Mixed venous oxygen saturation during cardiopulmonary bypass poorly predicts regional venous saturation. *Anesth Analg* 1995, **80**. 466–72

39 Vincent JL. Blood lactate levels· index of tissue oxygenation *Int J Intensive Care* 1998; **5**: 48–53

40 Elizalde JI, Hernández C, Llach J, et *al* Gastric intramucosal acidosis in mechanically ventilated patients: role of mucosal blood flow *Crit Care Med* 1998; **26**: 827–32

41 Hamilton Davies C, Mythen MG, Salmon JB, et *al.* Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry *Intensive Care Med* 1997; **23**: 276–81

42 Lebuffe G, Raingeval X, Decoene C, et *al.* Sigmoid tonometry in infrarenal abdominal aortic aneurysm (AAA) surgery. *Br J Anaesth* 1999; **82**: A149

43 Schlichtig R, Mehta N, Gayowski TJ. Tissue–arterial $P\text{CO}_2$ difference is a better marker of ischemia than intramucosal pH (pHi) or arterial pH–pHi difference. *J Crit Care* 1996; **11**· 51–6

44 Gardeback M, Settergren G, Ohquist G, et *al.* Effect of dopexamine on calculated low gastric intramucosal pH following valve replacement. *Acta Anaesthesiol Scand* 1995; **39**· 599–604

45 Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *Br J Anaesth* 1995, **74**. 591–606

46 Friedel N, Wenzel R, Matheis G, et *al.* Haemodynamic effects of different doses of dopexamine hydrochloride in low cardiac output states following cardiac surgery. *Eur Heart J* 1992; **13**: 1271–6

47 Hurley J, McDonagh P, Cahill M, et *al.* The hemodynamic effect of prophylactic peri-operative dopexamine in coronary artery bypass patients. *Eur Heart J* 1995; **16**: 1705–9

British Journal of Anaesthesia **84** (1)· 28–32 (2000)

Effects of changes in packed cell volume on the specific heat capacity of blood: implications for studies measuring heat exchange in extracorporeal circuits

A. S. T. Blake[1 3], G. W. Petley[1] and C. D. Deakin[2]*

[1]Department of Medical Physics and Bioengineering and [2]Shackleton Department of Anaesthetics, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
**Corresponding author*
[3]Present address: Magdalen College, Oxford OX1 4AU, UK

Extracorporeal circuits such as cardiopulmonary bypass (CPB) and renal dialysis machines cause active and/or passive loss of body heat. Attempts to quantify this heat loss are generally based on the Fick principle which requires knowledge of the specific heat capacity (SHC) of blood. As changes in packed cell volume are common, we investigated the effect of these changes on the SHC of blood over a range of packed cell volumes (PCV) from whole blood at 43.1% (3594 J kg^{-1} °C^{-1}) to pure Hartmann's solution (4153 J kg^{-1} °C^{-1}). The SHC of other fluids used during CPB was also measured and found to be 4139 J kg^{-1} °C^{-1} and 4082 J kg^{-1} °C^{-1} for normal saline and Gelofusine, respectively. The maximum variability in SHC over the range of PCV values encountered during CPB was calculated to be small (5.5%). We conclude that use of a constant value of SHC for calculation of thermal energy transfer is currently justified.

Br J Anaesth 2000; **84**: 28–32

Keywords: blood, specific heat capacity; blood, packed cell volume; heart, cardiopulmonary bypass; temperature, body; temperature, regulation

Accepted for publication: July 30, 1999

Postoperative hypothermia is common after hypothermic cardiopulmonary bypass (CPB).[1–4] Subjects undergoing such procedures are generally rewarmed until a normal core temperature is attained. However, core temperature correlates poorly with the adequacy of rewarming. Subsequently, postoperative hypothermia is common as heat is transferred from a warm core to cold periphery, and may increase postoperative morbidity. Thermal energy balance (TEB) has been proposed as an alternative index for assessing the adequacy of rewarming on bypass.[5] This is a calculation of the net thermal energy transferred to the patient during CPB. Therefore, during the cooling phase when energy is removed from the patient, TEB is negative. As the patient is rewarmed, energy is transferred to the patient so that TEB becomes progressively less negative until, at the end of bypass, the value of TEB reflects net energy transfer. TEB is calculated using the Fick principle, given in the following equation:

$$E(T) = c\rho \int_0^T \Delta\theta(t).Q(t)\mathrm{d}t \qquad (1)$$

where $E(T)$=net TEB at time $t=T$ (J); c=specific heat capacity of blood (J kg^{-1} °C^{-1}); r=density of blood (kg m^{-3}); $\Delta q(t)$=temperature difference across the perfusion circuit at time t (°C); and $Q(t)$=pump flow at time t (m^3 s^{-1}).

It can be seen from equation (1) that the value of specific heat capacity (SHC) of blood is required to calculate TEB using this method. Previous studies have reported net energy transfers for CPB procedures ranging from −389 kJ to 1247 kJ, despite similar rewarming procedures.[6 7] The correlation between TEB and other measures of rewarming such as coldest postoperative temperature and time to rewarm to 37°C are poor.[8] This suggests that TEB may be of limited value as an indicator of the adequacy of rewarming. The reason for this poor performance may be explained either by genuine variability or by errors. Errors can result from failure to account for all thermal energy losses/gains or from assumptions made for calculation of TEB. One assumption made is that SHC remains constant throughout CPB. As it is common practice for blood to be diluted with crystalloid solutions, packed cell volume (PCV) varies, typically over the range 30–45%, and it is possible that this may alter SHC and therefore lead to errors in the calculated value for TEB. Previous studies on both human and canine blood have reported that SHC varies with PCV[9 10] but have attained different PCV values by diluting blood with plasma. As blood is diluted with crystalloid solutions during CPB,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

the resulting SHC for a given PCV is likely to differ from that attained using a plasma diluent.

The aim of this study was to investigate the effect of these changes in the composition of blood on calculation of TEB. Accordingly, the relationship between the SHC of blood and PCV, diluting with Hartmann's solution, and the SHC of other fluids given during CPB were measured.

Methods

Background theory

The SHC (c) of the fluid under test was determined experimentally by heating it inside a calorimeter.

SHC is given by the formula:

$$E = mc\Delta T \qquad (2)$$

where E=energy added to system (J); m=mass of fluid (g); c=specific heat capacity (J kg^{-1} °C^{-1}); and ΔT=resultant change in temperature (°C).

In practice, the thermal energy added to the system not only heats the fluid but also heats the apparatus and surrounding environment. To account for losses to the apparatus, the heat capacity of the apparatus was determined through measurements on a fluid of known SHC. Thermal losses to the environment were reduced by insulating the apparatus and by immersing it in a waterbath set at a similar temperature to that of the fluid under investigation, thereby minimizing thermal gradients. Despite these precautions, some heat transfer from the fluid is likely and these errors were accounted for using the substitution method in which the heating characteristics of a fluid of known SHC, in this case distilled water, were first measured. The water was then substituted with the fluid under investigation. The SHC of this fluid may then be calculated using the equation derived in appendix 1.

$$c_f = \frac{(m_w c_w + C)\,\dfrac{dT_w}{dt}\,P_f}{P_w m_f\,\dfrac{dT_f}{dt}} - \frac{C}{m_f} \qquad (3)$$

where c_f=specific heat capacity of fluid (J kg^{-1} °C^{-1}); m_w= mass of water (kg); c_w=specific heat capacity of water (J kg^{-1} °C^{-1}); C=heat capacity of the apparatus (J °C^{-1}); dT_w/dt=rate of change of water temperature with time (°C s^{-1}); P_f =electrical power supplied to fluid (W); P_w= electrical power supplied to water (W); m_f =mass of fluid (kg); and dT_f/dt=rate of change of fluid temperature with time (°C s^{-1}).

Apparatus

The apparatus was set up as shown in Figure 1. A vacuum flask holding approximately 600 ml of fluid was used as a calorimeter. The flask was fitted with a polystyrene lid and covered with a polystyrene cap to reduce thermal losses. Thermal gradients across the flask were reduced by immersing it in a thermoregulated water bath set at 37±0.1°C. A magnetic stirrer was used to ensure adequate mixing of the fluid within the vacuum flask. The fluid was heated in the vacuum flask using a 15 W resistor connected to a d.c. supply. The current flowing through the resistor and the voltage across it were measured using calibrated multimeters, so that the electrical power supplied to the fluid was calculated using the formula:

$$P = IV \qquad (4)$$

where P=electrical power (W); I=current (A); and V= voltage (V).

The temperature of the fluid was measured using a calibrated mercury-in-glass thermometer with a resolution of 0.01°C and maximum error of 0.04°C over the range used. The rate of change in temperature was found by measuring the time taken to heat the fluid between 36 and 38°C. The heat capacity of the apparatus was found to be 135 J °C^{-1} (see appendix 2).

Measurements

Blood (600 ml) was obtained from a healthy male volunteer. To prevent clotting, 2 ml of concentrated heparin 5000 u. were added. All blood measurements were performed on the same day as donation. Measurements of SHC were made at four different PCV values, diluting with Hartmann's solution. After each dilution, PCV was measured, taken as the average of five measurements, using a Radiometer ABL505 and OSM3. For completeness, the SHC of other fluids used during CPB, namely normal saline, Hartmann's solution and Gelofusine, was also determined.

The repeatability of the apparatus was determined by making multiple measurements on all fluids except those involving blood and is expressed as a percentage coefficient of variation (%cv).

$$\%\text{cv} = 100 \times (\text{SD}/\text{mean}) \qquad (5)$$

The accuracy of the apparatus was assessed by measuring the SHC of two known standards with SHC predicted to be at the upper and lower limits of the fluids to be investigated. Because of cost, availability and ease of use, distilled water (4180 J kg^{-1} °C^{-1}) and sodium chloride 2.77 mol litre^{-1} (3604 J kg^{-1} °C^{-1}) were used. It should be noted, however, that distilled water was also used to characterize the apparatus. The relationship between SHC and PCV was determined using the regression function within Microsoft Excel v. 5.0a.

Results

There was good agreement between SHC values measured with the apparatus and those predicted from the literature, with an acceptable repeatability (Table 1). Measurements

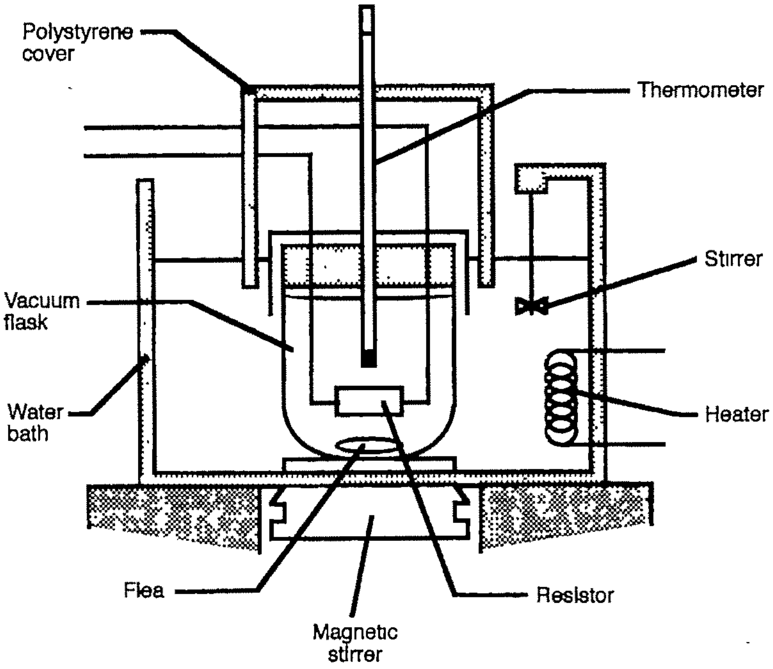


Fig 1 The apparatus.

Table 1 Comparison of measurements with those in the literature SHC=Specific heat capacity, SD=standard deviation; CV=coefficient of variation

Sample	Measured SHC (J kg^{-1} °C^{-1})	'Textbook' SHC (J kg^{-1} °C^{-1})	SD (J kg^{-1} °C^{-1})	CV (%)	No. of measurements
Distilled water	4179	4180[11]	13	0.32	7
Sodium chloride 2.77 mol litre^{-1}	3604	3604[12]	27	0.75	10

Table 2 Measurements of SHC made on fluids encountered during CPB SHC=Specific heat capacity; SD=standard deviation; CV=coefficient of variation

Sample	SHC (J kg^{-1} °C^{-1})	SD (J kg^{-1} °C^{-1})	CV (%)	No. of measurements
Normal saline	4139	30	0.72	7
Gelofusine	4082	17	0.47	5
Hartmann's solution	4153	15	0.38	9
Whole blood	3594	16	0.45	4

Table 3 Calculated specific heat capacity (SHC) at the extremes of the range of packed cell volume (PCV) values typically encountered during CPB

PCV (%)	Calculated SHC (J kg^{-1} °C^{-1})
30	3754
45	3559

of the SHC of fluids encountered during CPB are summarized in Table 2.

Whole blood was found to have a PCV of 43.1%. This was later diluted with Hartmann's solution to achieve a range of PCV values of 43.1% to 0% (pure Hartmann's solution). At each PCV, SHC was measured (Fig. 2). There

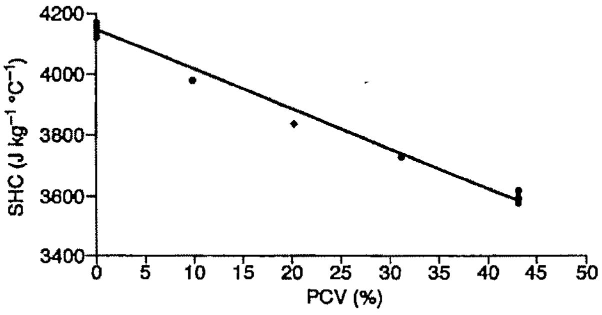


Fig 2 Relationship between specific heat capacity (SHC) and packed cell volume (PCV)

was a linear relationship between SHC and PCV ($r^2=0.99$, $P<0.001$):

Specific heat capacity (J kg^{-1} °C^{-1}) =

$$4146.7-13.1\times\text{packed cell volume }(\%)$$

Using this formula, the SHC of blood over the range of PCV values encountered during CPB was calculated (Table 3). This change in PCV equates to a maximum variation in SHC of 5.5%.

Discussion

Our measurements suggest that changes in the SHC of blood during CPB are small and are unlikely to account for the variability in TEB reported in the literature. During CPB it may be expected that the maximum change in the SHC of blood and therefore resulting error in TEB is approximately 5.5%. Results for net energy transfer reported in the literature vary from –389 kJ to 1247 kJ, despite similar rewarming procedures.[6 7] Errors caused by changes in the SHC of blood are small in comparison and are unlikely to be an explanation for these results. Therefore, it is currently acceptable to use a constant value for SHC for calculation of TEB. As the SHC of normal saline and Gelofusine are similar to that of Hartmann's solution, their use in place of Hartmann's solution is likely to result in similar changes in the SHC of blood and is therefore unlikely to alter the conclusions of the study.

Making accurate corrections for SHC in the calculation of TEB requires regular measurement of PCV as fluids added to blood during CPB are absorbed relatively rapidly. The practical difficulties in measuring PCV during CPB and integrating the results into the TEB equation are probably not justified in the light of the small changes in SHC that occur with haemodilution.

The performance of the apparatus has been shown to be sufficiently accurate by making measurements on fluids of known SHC, and by making repeat measurements. The results for sodium chloride 2.77 mol litre^{-1} agreed well with those reported previously in the literature, and measurements on distilled water confirmed the stability of the calibration of the system. Repeat measurements for all fluids gave a maximum reproducibility error (%cv) of 0.75%.

The SHC of whole blood measured in this study (3594 J kg^{-1} °C^{-1}) agreed well with that published previously by Mendlowitz[9] (3600 J kg^{-1} °C^{-1}) on human blood. Dilution of blood with Hartmann's solution demonstrated that SHC increased linearly as PCV was reduced. While this finding was also reported by Epstein and colleagues[10] using canine blood, the gradients of the two studies differ, with Epstein and colleagues reporting –7.2 J kg^{-1} °C^{-1} %$^{-1}$, compared with –13.1 J kg^{-1} °C^{-1} %$^{-1}$ found in this study. This difference is likely to reflect the use of plasma and Hartmann's solution to dilute blood in the respective studies.

Calculation of TEB also requires a value for the density of blood which, in common with SHC, varies with PCV and haemodilution. However, these variations in density and SHC occur in opposite directions,[10] so the correction to TEB for both density and SHC is smaller than the correction for SHC alone. Therefore, the SHC error of 5.5% presented in this analysis represents a worst case estimate of the true error in calculating TEB using constant physical properties for blood.

Variability in reported values for the net transfer of energy during CPB can be explained either by genuine changes or by errors. Variability between patients may occur for several reasons. The approach assumes that all patients are similarly normothermic at the onset of CPB. In practice, the patient has been anaesthetized for approximately 30–60 min before commencing CPB and has lost heat. This is reflected in the variability of core temperature which decreases to a mean value of 35.3 (SD 0.8)°C before commencing CPB.[8] During the rewarming phase, heat redistribution from the core to the periphery is impeded by vasoconstriction and microcirculatory dysfuction.[13] Variability between patients in the rate of this heat redistribution and in the size of the core affects TEB.

In addition to errors caused by calculation of TEB, errors may also be attributed to thermal energy losses/gains not accounted for by the Fick technique, which assumes that all energy changes are a result of the bypass circuit. In practice, an open thorax results in losses of thermal energy to the ambient environment. Losses also occur from the remainder of the patient and from tubing connecting the patient to the bypass equipment. It is also likely that the patient generates some heat.

The Fick principle has also been applied to assess energy losses associated with renal dialysis in an intensive care setting.[14 15] Changes in the composition of blood and, in particular, plasma, as a result of this procedure may lead to changes in the SHC of blood. However, we failed to demonstrate large changes in the SHC of blood with changing PCV and differences between the SHC of the different colloids and crystalloids measured were also small. It is therefore likely that a constant value for the SHC of blood is also appropriate for thermal energy transfer studies involving renal dialysis.

In summary, we have shown that the errors in calculation of TEB caused by changes in the SHC of blood during CPB are small compared with the variability in values for the net energy transfer published in the literature Therefore, currently the use of a constant value for the SHC of blood is adequate when calculating TEB.

Appendix 1

Equation (2) was modified to account for the residual heat capacity of the apparatus and the thermal losses to the surrounding environment·

$$p=(mc+C)\frac{dT}{dt}+k \qquad (6)$$

where p=thermal power supplied to the calorimeter (W), m=mass of fluid (kg), c=specific heat capacity of fluid (J kg^{-1} °C^{-1}), C=heat capacity of

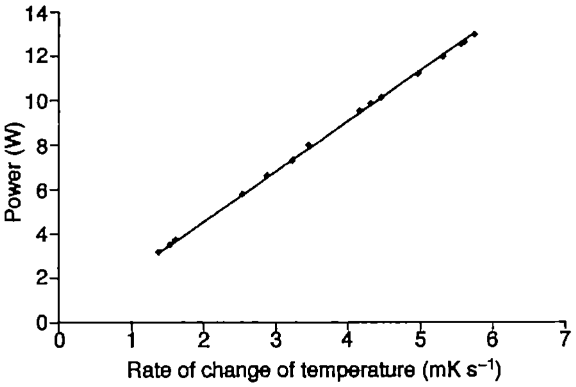


Fig 3 Rate of increase in the temperature of water as a function of input power.

the apparatus (J °C^{-1}), dT/dt=rate of change of temperature with time (°C s^{-1}), and k=thermal loss to the surrounding environment (W).

It may be assumed that electrical power supplied to the system is approximately equal to the thermal power heating it and therefore:

$$p_f = \frac{P_f}{P_w} p_w \tag{7}$$

where p_f=thermal power supplied to fluid, as defined by equation (6) (W), P_f=electrical power supplied to fluid, as defined by equation (4) (W); P_w=electrical power supplied to water, as defined by equation (4) (W), and p_w=thermal power supplied to water, as defined by equation (6) (W) Substituting from equation (6), we get:

$$(m_f c_f + C) \frac{\mathrm{d}T_f}{\mathrm{d}t} + k_f = \frac{P_f}{P_w} \left\{ (m_w c_w + C) \frac{\mathrm{d}T_w}{\mathrm{d}t} + k_w \right\} \tag{8}$$

$$c_f = \frac{(m_w c_w + C) \frac{\mathrm{d}T_w}{\mathrm{d}t} P_f}{P_w m_f \frac{\mathrm{d}T_f}{\mathrm{d}t}} - \frac{C}{m_f} - \frac{k_f - \frac{P_f}{P_w} k_w}{m_f \frac{\mathrm{d}T_f}{\mathrm{d}t}} \tag{9}$$

But, if losses are minimized through insulation and minimizing thermal gradients using a water bath, then the last term becomes negligibly small Therefore, the equation may be reduced to

$$c_f = \frac{(m_w c_w + C) \frac{\mathrm{d}T_w}{\mathrm{d}t} P_f}{P_w m_f \frac{\mathrm{d}T_f}{\mathrm{d}t}} - \frac{C}{m_f} \tag{10}$$

Appendix 2

The heat capacity of the apparatus was found by heating 500 g of distilled water in the calorimeter and measuring the rate of temperature increase for a range of power inputs. Power was plotted against the rate of change of temperature (Fig. 3).

Using equation (6), the gradient of the line (2224 °C s^{-1}) is equal to $m_w c_w + C$. As c_w=4180 J kg^{-1} °C^{-1},[12] and m_w=0.5 kg, the heat capacity of the apparatus C=135 J °C^{-1}

Acknowledgements

We thank Mr F Clewlow, Mr S. Clitheroe and Mr P. Willcocks for technical assistance and helpful discussion throughout the study

References

1 Noback CR, Tinker JH. Hypothermia after cardiopulmonary bypass in man: amelioration by nitroprusside induced vasodilation during rewarming. *Anesthesiology* 1980; **53**: 277–80

2 Jani K, Carli FM, Bidstrup BP, Royston D. Prevention of body temperature reduction (afterdrop) following hypothermic perfusion. *Perfusion* 1988; **3**: 301–6

3 Duthie DJR, Woolman PS, Doyle AR. Enoximone and warming after hypothermic cardiopulmonary bypass *Br J Anaesth* 1995; **75**: 43–6

4 Deakin CD, Petley GW, Smith D. Pharmacological vasodilation improves efficiency of rewarming from hypothermic cardiopulmonary bypass. *Br J Anaesth* 1998; **81**: 147–51

5 Davis FM, Parimelazhagan KN, Harris EA. Thermal balance during cardiopulmonary bypass with moderate hypothermia in man. *Br J Anaesth* 1977; **49**: 1127–32

6 Jenkins I, Karliczek G, De Geus F, Brenken U. Postbypass hypothermia and its relationship to the energy balance of cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1991; **5**: 135–8

7 Pujol A, Fusciardi J, Ingrand P, Baudouin D, Le Guen AF, Menu P. Afterdrop after hypothermic cardiopulmonary bypass: The value of tympanic membrane temperature monitoring. *J Cardiothorac Vasc Anesth* 1996, **10**: 336–41

8 Deakin CD, Clewlow F, Petley GW. Measurement of rewarming from hypothermic cardiopulmonary bypass: A review. *Cardiovasc Eng* 1998; **3**; 36–42

9 Mendlowitz M. The specific heat of human blood. *Science* 1948: **107**; 97–8

10 Epstein W, Visscher MB, Stish R, Ballen H. Specific heat of canine blood. *J Appl Physiol* 1963; **18**: 843–4

11 Kaye GWC, Laby TH. *Tables of Physical and Chemical Constants*, 14th Edn. London: Longman, 1973; 54–5

12 Washburn EW *International Critical Tables for Numerical Data Physics, Chemistry and Technology*. New York: McGraw Hill, 1929; **5**: 115

13 Keller MW, Geddes L, Spotnitz W, Kaul S, Duling BR. Microcirculatory dysfuntion following perfusion with hyperkalemic, hypothermic, cardioplegic and solutions and blood reperfusion. *Circulation* 1991; **84**: 2485–94

14 Booth MG. Fox C, Dobb G. Energy losses from continuous venovenous haemofiltration (an *in vitro* study). *Br J Anaesth* 1995; **74**: A359

15 Booth MG, Fox C, Dobb G. Energy losses associated with continuous venovenous haemodiafiltration in intensive care patients. *Br J Anaesth* 1995; **74**: A360

British Journal of Anaesthesia 84 (1): 33–7 (2000)

Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients†

O. Detsch, G. Schneider, E. Kochs*, G. Hapfelmeier and C. Werner

Klinik für Anaesthesiologie, Klinikum rechts der Isar, Technische Universität München,
Ismaningerstr. 22, D-81675 München, Germany
**Corresponding author*

We have studied the effects of increases in isoflurane concentration on the EEG bispectral index (BIS) in 70 patients anaesthetized with isoflurane–nitrous oxide–sufentanil for major abdominal surgery. During surgery, baseline BIS was recorded at 0.8% end-tidal isoflurane with nitrous oxide in oxygen ($F_{I_{O_2}}$ 0.35). After this, end-tidal isoflurane was increased to 1.6% for 15 min and decreased subsequently to 0.8% for 20 min to assess recovery. In 20 patients, BIS decreased from a mean value of 40 (SD 9) during baseline to 25 (10) at 1.6% isoflurane. In contrast, BIS did not change in 23 patients and increased in 27 patients from 35 (6) to 46 (8) as isoflurane was increased to 1.6%. In all patients, BIS recovered to baseline values at 0.8% isoflurane. The changes in BIS with increasing isoflurane concentration were not related to drugs or differences in physiological variables, which did not differ between groups. Patients with a decrease in BIS were significantly younger (38 (range 18–68) yr) than those with unchanged (55 (26–70) yr) or increased (60 (40–70) yr) BIS values ($P<0.001$). It is possible that the paradoxical increase in BIS is related to continuous pre-burst EEG patterns consisting of high-frequency activity. This suggests that the use of BIS as a guide for isoflurane administration may be misleading in some patients undergoing surgical procedures.

Br J Anaesth 2000; **84**: 33–7

Keywords: anaesthesia, depth; anaesthetic techniques, inhalation; anaesthetics volatile, isoflurane; monitoring, electroencephalography; monitoring, bispectral index

Accepted for publication: August 10, 1999

Previous studies have shown that several variables from the processed EEG correlate with clinical measures of depth of anaesthesia.[1 2] For example, the EEG-derived bispectral index (BIS) appears to be sensitive to the hypnotic component of anaesthesia.[3] As a consequence, BIS has been introduced into clinical practice to guide administration of volatile anaesthetics.[4 5]

BIS decreases with increasing concentration of anaesthetic (i.e. as depth of anaesthesia increases). BIS values of 90–100 are present in the awake individual and BIS=0 during EEG isoelectricity.[2 6] We observed that BIS increased during increasing end-tidal isoflurane concentration in some surgical patients during routine intraoperative EEG monitoring. Therefore, in this study we systematically investigated the effects of low and high isoflurane concentrations (i.e. different levels of depth of anaesthesia) on the raw EEG and BIS during isoflurane–nitrous oxide–sufentanil anaesthesia.

Patients and methods

After obtaining approval from the Institutional Review Board, we studied prospectively 70 patients (aged 18–70 yr; ASA I–III) of both sexes (33 females, 37 males) undergoing elective abdominal surgery. Patients had no history of neurological or psychiatric disorders. After oral premedication with midazolam, anaesthesia was induced with propofol 1.5–2.0 mg kg^{-1} and sufentanil 0.2–0.3 µg kg^{-1}. Atracurium 0.5 mg kg^{-1} was administered for neuromuscular block which was monitored using a nerve stimulator The trachea was intubated and the lungs ventilated with 65% nitrous oxide in oxygen using a semi-closed system with a fresh gas flow of 6 litre min^{-1}. Ventilation was adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.5–5.0 kPa. Before the study, isoflurane was set at 0.8%. Sufentanil was given according to general clinical assessment (haemodynamic responses, sweating, lacrimation). Non-invasive or invasive mean arterial pressure (MAP), electrocardiographic heart rate (HR), pulse oximetry (Sp_{O_2}) and nasopharyngeal temperature were monitored continuously.

Body temperature was maintained using heating blankets.

---

†Presented in part at the annual meeting of the American Society of Anesthesiologists, Orlando, USA, October 1998

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Norepinephrine (range 0–10 µg min^{-1}) was given i.v. if needed to maintain arterial pressure.

EEG recording

EEG recordings (two-channel referential montage; impedances <2 kΩ) were performed using surface electrodes (according to the international 10–20 system) placed at F7 and F8, with Fz as the reference and Fp1 as the ground. All quantitative EEG (QEEG) and electromyographic (EMG) data were averaged from the bifrontal leads. The EEG/EMG data were obtained using an Aspect A 1000 monitor (BIS v. 3.12, Aspect Medical Systems Inc., Natick, USA). The low pass was set at 0.25 Hz, no high pass was used, and the notch filter was enabled. The raw EEG was digitized continuously at 256 Hz per channel. QEEG/EMG variables were stored on a microcomputer at 5-s intervals. The burst suppression ratio (BSR) was calculated as the percentage of isoelectric periods occurring over the last 63 s. The burst-compensated spectral edge frequency 95% (BcSEF)[2] was calculated off-line as:

$$\mathrm{BcSEF}=\mathrm{SEF}\times\left(1-\frac{\mathrm{BSR}}{100}\right)$$

Electromyographic activity was calculated as absolute power (dB) in the 70–300 Hz (EMG high) and 70–110 Hz (EMG low) power bands.

Study interval

At least 15 min after skin incision and the last sufentanil dose (0.2 µg kg^{-1}), the end-tidal isoflurane concentration was adjusted and maintained constant at 0.8% for 20 min and baseline recordings were performed. End-tidal isoflurane was then increased rapidly to 1.6% for 15 min and all measurements repeated. Subsequently, the end-tidal isoflurane concentration was decreased rapidly to 0.8% for 20 min to assess recovery. No additional drugs were given over the study period.

Data analysis

EEG and EMG data, and physiological variables (MAP, HR, Sp_{O_2}, body temperature measured at 1-min intervals) were averaged from the last 5 min of each phase (baseline, 1.6% isoflurane, recovery). The BIS response to increased isoflurane was retrospectively classified as 'BIS decrease' (mean BIS at 1.6% isoflurane < mean BIS–2 SD at 0.8% isoflurane), 'BIS constant' (mean BIS at 1.6% isoflurane= mean BIS±2 SD at 0.8% isoflurane) or 'BIS increase' (mean BIS at 1.6% isoflurane > mean BIS+2 SD at 0.8% isoflurane). Data are given as mean (SD). For statistical analysis, multiple Friedman and Kruskal–Wallis tests followed by Wilcoxon and Mann–Whitney *U* tests were performed, as appropriate. ASA status, sex, number of patients with BSR = 0 (at 1.6% isoflurane) and number of patients requiring norepinephrine (at 1.6% isoflurane) were compared using chi-square tests. A Bonferroni-adjusted $P<0.05$ was considered significant.

Table 1 Quantitative EEG and EMG data during baseline (0.8% end-tidal isoflurane), 1.6% isoflurane and recovery (0.8% isoflurane): bispectral index (BIS), burst suppression ratio (BSR) and burst-compensated spectral edge frequency 95% (BcSEF) (mean (SD)) *$P<0.05$ *vs* baseline; †$P<0.05$ *vs* 'BIS increase'; ‡$P<0.05$ *vs* 'BIS constant'

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
BIS			
Baseline	35 (6)	36 (6)	40 (9)
Isoflurane 1.6%	46 (8)*	37 (7)†	25 (10)*†‡
Recovery	35 (6)	34 (4)	39 (8)
BSR (%)			
Baseline	0 (0)	0 (2)	0 (0)
Isoflurane 1.6%	10 (9)*	8 (10)*	14 (27)*
Recovery	0 (0)	0 (1)	0 (0)
BcSEF (Hz)			
Baseline	8.2 (2.9)	8.4 (1.7)	12.0 (4.0)†‡
Isoflurane 1.6%	8.0 (2.2)	5.5 (1.1)*†	5.7 (2.3)*†
Recovery	8.7 (4.1)	9.3 (2.3)	11.5 (4.4)
EMG high (dB)			
Baseline	45 (4)	44 (4)	45 (4)
Isoflurane 1.6%	44 (3)	44 (3)	46 (5)
Recovery	43 (2)	43 (2)	43 (1)
EMG low (dB)			
Baseline	31 (5)	31 (5)	31 (6)
Isoflurane 1.6%	30 (4)	31 (4)	33 (7)
Recovery	28 (3)	30 (4)	30 (2)

Results

EEG data are summarized in Table 1. In 20 patients, BIS decreased with increasing isoflurane concentration (BIS decrease group) and was unchanged in 23 patients (BIS constant group). In 27 patients (BIS increase group), BIS increased significantly (maximum increase 195%). Changes in BIS with increased isoflurane concentration occurred 5–8 min after the increase in isoflurane and remained stable until isoflurane was decreased for assessment of recovery. During baseline or recovery, no burst suppression patterns were detected in any patient. With 1.6% isoflurane the burst suppression ratio did not differ significantly between groups (Table 1). The number of patients with no detected isoelectric periods (BSR=0) during 1.6% isoflurane differed significantly between groups (BIS increase six of 27; BIS constant eight of 23; BIS decrease 12 of 20) ($P<0.02$).

Figure 1 shows the time course of a typical EEG response (increasing BIS) to increased inspired isoflurane in a patient with EEG burst suppression patterns. Figure 2 shows the raw EEG tracings of patients with increasing (Fig. 2A) and decreasing (Fig. 2B) BIS in response to increased isoflurane. EMG baseline values or the time course of EMG values did not differ significantly between groups. EEG and EMG values during recovery did not differ from baseline values.

Table 2 shows patient data, sufentanil dose and norepinephrine infusion rates. Patients with a decreased BIS were significantly younger than those with unchanged or

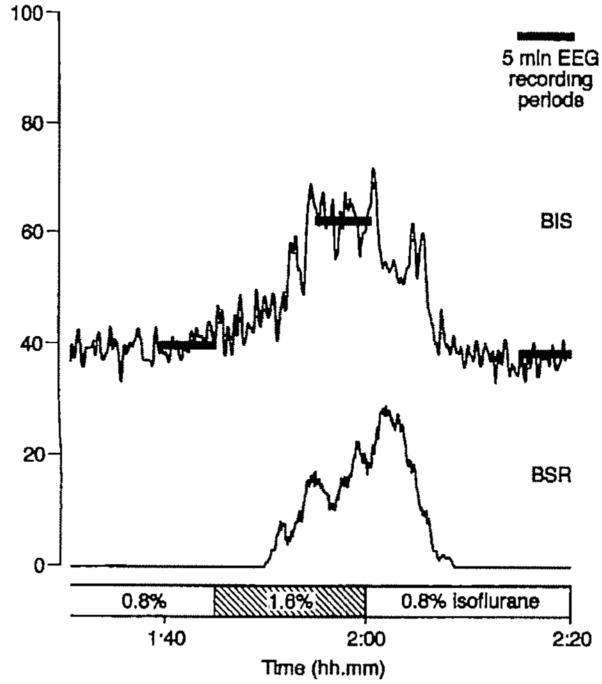


Fig 1 Representative EEG response (bispectral index (BIS) upper panel; burst suppression ratio (BSR) lower panel) to increasing isoflurane from 0.8% (mean baseline BIS 39 (SD 2)) to 1.6% (BIS 62 (3)) and recovery after a decrease to 0.8% isoflurane (BIS 38 (2)). In this patient, the EEG response was classified as a 'BIS increase' as BIS (62) during 1.6% isoflurane exceeded mean baseline BIS +2 SD (43) at 0.8% isoflurane.

increased BIS values ($P<0.001$). There were no differences in sex, ASA status or total sufentanil dose between groups. There were no significant differences in norepinephrine infusion rates or number of patients given norepinephrine (at 1.6% isoflurane) between groups. No patient needed an infusion of norepinephrine for MAP support during baseline or recovery.

Table 3 shows physiological variables over time. There were no differences in the time course of physiological variables between groups and recovery values did not differ significantly from baseline.

Discussion

We found significant increases in BIS in approximately 40% of patients and unchanged BIS values in 33% during major abdominal surgery when the anaesthetic concentration was increased from 0.8% to 1.6% end-tidal isoflurane. This EEG pattern is a paradoxical BIS response, as BIS is supposed to decrease continuously with increasing anaesthetic concentration.[2 6 7]

In general, the characteristic EEG effect of increasing concentrations of volatile anaesthetic is a progressive slowing until burst suppression patterns occur.[8–10] The progressive EEG depression should be reflected by the QEEG variables in order to consider these as reasonable values for monitoring anaesthetic dose and depth. The EEG variable BIS was introduced recently into clinical practice as a measure of the hypnotic effect of anaesthetics.[2] Numerous studies have demonstrated a close correlation of BIS and various clinical measures of depth of anaesthesia, despite the fact that these lack sensitivity and specificity.[3 6 11] Some have suggested that the concentration of anaesthetics (including volatile anaesthetics) should be adjusted according to changes in BIS.[4 5 12] However, our results challenge the concept of administration of anaesthetics guided by BIS as BIS may increase paradoxically when isoflurane concentration is increased.

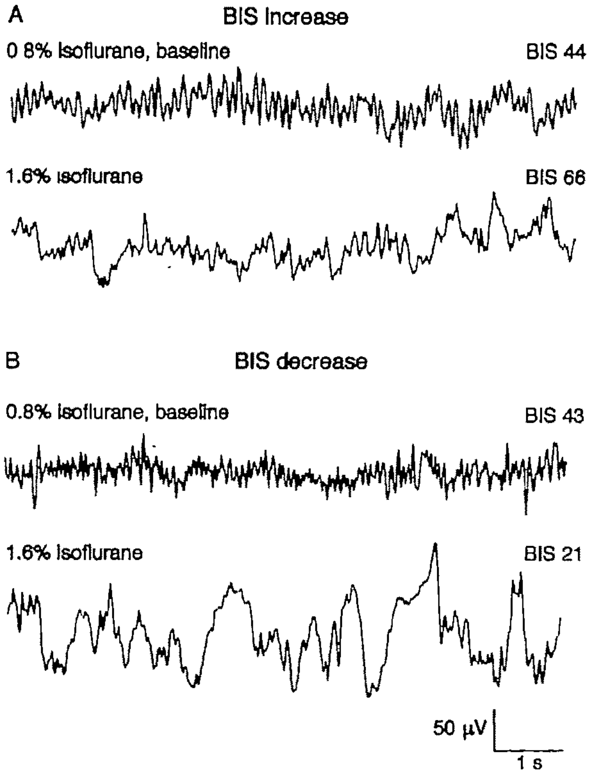


Fig 2 Characteristic raw EEG signals (approximately 8 s each) of two patients (one in the 'BIS increase' group (A) and one in the 'BIS decrease' group (B)) during baseline (0.8% isoflurane) and during the increase in isoflurane to 1.6%. The raw signals are representative for the preceding 5 min of EEG activity in both patients. Note that in both patients, no isoelectric periods were present.

The BIS algorithm combines a variety of calculated EEG sub-parameters[2] which have not been published in detail. Although the underlying mechanisms of a paradoxical BIS increase remain speculative, some mathematical limitations may apply. In patients undergoing hypothermic cardiopulmonary bypass (propofol and alfentanil background anaesthetic), during cooling (<32°C), BIS values were considerably variable and sometimes overlapped with awake values. Also, high BIS values (>60) were associated with the occurrence of EEG burst suppression patterns and the authors suggested that the algorithm was insufficient to calculate BIS in the presence of isoelectric periods.[13] These authors examined the same BIS version (v. 3.12) as used here. However, the BIS algorithm seems to include burst suppression patterns via two separate calculations, BSR and

Table 2 Patient data and sufentanil doses in the 'BIS increase', 'BIS constant' and 'BIS decrease' groups (mean (SD or range)) Norepinephrine infusion rate for MAP support (>70 mm Hg) and number of patients who received norepinephrine infusion during administration of 1.6% isoflurane are shown (mean (SD) and number) †$P<0.001$ *vs* 'BIS increase', ‡$P<0.001$ *vs* 'BIS constant'

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
Age (yr)	60 (40–70)	55 (26–70)	38 (18–68) †‡
Sex (F/M)	11/16	11/12	11/9
ASA status (I/II/III)	9/17/1	5/16/2	8/10/2
Height (cm)	170 (9)	170 (9)	173 (12)
Weight (kg)	75 (14)	77 (13)	72 (16)
Total sufentanil (μg kg^{-1})	0.6 (0.2)	0.6 (0.4)	0.5 (0.3)
Norepinephrine (μg min^{-1})	2.8 (4.0)	1.2 (2.0)	1.0 (2.6)
(No.)	(11)	(7)	(5)

Table 3 Physiological variables during baseline (0.8% end-tidal isoflurane), 1.6% isoflurane and recovery (0.8% isoflurane). heart rate (HR), mean arterial pressure (MAP), pulse oximetry (Sp_{O_2}) and nasopharyngeal temperature (mean (SD)) *$P<0.05$ *vs* baseline

	BIS increase ($n=27$)	**BIS constant ($n=23$)**	**BIS decrease ($n=20$)**
HR (beat min^{-1})			
Baseline	70 (14)	73 (11)	69 (14)
Isoflurane 1.6%	72 (13)	77 (13)	76 (14)
Recovery	72 (16)	78 (10)	76 (15)
MAP (mm Hg)			
Baseline	87 (16)	85 (13)	84 (14)
Isoflurane 1.6%	76 (4)*	77 (7)*	76 (6)*
Recovery	84 (13)	93 (16)	88 (11)
Sp_{O_2} (%)			
Baseline	98 (1)	98 (1)	98 (1)
Isoflurane 1.6%	98 (1)	98 (1)	98 (1)
Recovery	98 (1)	98 (1)	98 (1)
Temperature (°C)			
Baseline	35.3 (0.5)	35.2 (0.5)	35.3 (0.5)
Isoflurane 1.6%	35.1 (0.6)	35.2 (0.5)	35.1 (0.6)
Recovery	35.1 (0.6)	35.2 (0.6)	35.1 (0.6)

the 'QUAZI suppression index'.[2] It is unlikely that in our study a simple algorithm failure could explain the increase in BIS as BSR did not differ between groups. Furthermore, with 1.6% isoflurane, in all three groups there were patients with a BSR of 0 (i.e. without isoelectric periods). Visual inspection of the raw EEG tracings confirmed the absence of isoelectric periods in patients with a BSR of 0 (see Fig. 2).

Patients showing paradoxical BIS responses were significantly older than patients with decreases in BIS. As age is an important variable in isoflurane requirements,[14 15] the susceptibility to EEG effects of isoflurane may increase with age.[16 17] This is reflected by markedly higher baseline BcSEF in the 'BIS decrease' group. Similarly, the number of patients without isoelectric periods during 1.6% isoflurane was higher in younger patients. This supports the notion of increased susceptibility to isoflurane with age and thus the greater probability of causing proper burst suppression patterns during 1.6% isoflurane. The increase in BIS in patients with no isoelectric periods may be caused by continuous 'pre-burst' patterns in the EEG (i.e. the EEG shows continuous bursts without intermingled isoelectric periods). As high-frequency EEG activity is preserved or even increased during bursts,[2 9 18] BIS remains unchanged or increases. In pigs, paroxysmal alpha and beta activity was recorded during 1.5% isoflurane, which was also observed frequently in this study.[10] This phenomenon could be the correlate of a pre-burst EEG state. As patients with the paradoxical BIS increase were older, these patients were more likely to develop such a pre-burst state. We used BIS v. 3.12. It is not clear if the latest version of BIS software (v. 3.3) recognizes described EEG patterns and hence avoids displaying misleading information to the anaesthetist.

Our hypothesis that a paradoxical BIS response is caused by a pre-burst pattern is supported by the fact that the BcSEF did not change in the BIS increase group. As SEF95% is sensitive to burst suppression phenomena, we used burst-compensated SEF to allow for computation of SEF in the presence of isoelectric periods.[2 18] Interestingly, in addition to BIS, BcSEF also showed a paradoxical response in some patients.

Several confounding factors may have been present during our study. The EEG recordings were made during surgery. However, the observed differences in EEG responses are unlikely to be related to differences in surgical stimulation as there was no difference in the type of surgery (abdominal surgery) and the EEG recording was started after opening of the peritoneal cavity. Thus there was constant stimulation but no prominent stimulus. This is consistent with previous data showing no effect of ongoing surgery on the EEG during isoflurane anaesthesia.[19] In addition, the subsequent return to baseline data after a decrease in isoflurane supports the hypothesis that the observed changes were independent of changes in surgical stimulation.

Our results are not related to changes in physiological variables which did not differ between groups. There were no significant differences in mean norepinephrine dose or in the number of patients given norepinephrine. As there were patients who did not receive norepinephrine in all three groups, a direct interaction between norepinephrine infusion and EEG response is unlikely. In addition, norepinephrine has little effect on cerebrovascular resistance and does not cross the intact blood–brain barrier.[20] Thus the effects of norepinephrine are not a major mechanism of a paradoxical BIS increase. It is possible that the increase in BIS is related to an increase in high frequency activity (i.e. EMG activity). However, there were no differences in EMG activities between groups. Thus it is also unlikely that this factor contributed to the paradoxical BIS response.

In summary, our results indicate that increasing concentrations of isoflurane may induce paradoxical BIS increases during surgery using an isoflurane–nitrous oxide–sufentanil anaesthetic technique in some patients. It is unclear if the increase in BIS in patients without isoelectric periods reflects continuous pre-burst EEG activity consisting of high-frequency waves. Irrespective of the underlying mechanism, the presence of paradoxical BIS responses challenges the concept of monitoring depth of anaesthesia during isoflurane anaesthesia using the BIS technique.

References

1 Schneider G, Sebel PS. Monitoring depth of anaesthesia. *Eur J Anaesthesiol* 1997, **14** (Suppl. 15): 21–8

2 Rampil IJ. A primer for EEG signal processing during anesthesia. *Anesthesiology* 1998; **89**: 980–1002

3 Sebel PS, Lang E, Rampil IJ, *et al.* A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; **84**: 891–9

4 Guignard B, Menigaux C, Coste C, Chauvin M. Does bispectral EEG analysis change isoflurane administration during anesthesia in surgical patients? *Anesthesiology* 1997; **87**. A447

5 Song D, Joshi GP, White PF. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. *Anesthesiology* 1997; **87**: 842–8

6 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

7 Olofsen E, Dahan A. The dynamic relationship between end-tidal sevoflurane and isoflurane concentrations and bispectral index and spectral edge frequency of the electroencephalogram. *Anesthesiology* 1999; **90**. 1345–53

8 Pauca AL, Dripps RD. Clinical experience with isoflurane (Forane) Preliminary communication *Br J Anaesth* 1973; **45**: 697–703

9 Clark DL, Hosick EC, Adam N, Castro AD, Rosner BS, Neigh JL. Neural effects of isoflurane (Forane) in man. *Anesthesiology* 1973; **39**: 261–70

10 Rampil IJ, Weiskopf RB, Brown JG, *et al.* I653 and isoflurane produce dose-related changes in the electroencephalogram of pigs. *Anesthesiology* 1988; **69**: 298–302

11 Kearse LA, Rosow C, Zaslavsky A, Connors P, Dershwitz M, Denman W. Bispectral analysis of the electroencephalogram predicts conscious processing of information during propofol sedation and hypnosis. *Anesthesiology* 1998; **88**: 25–34

12 Gan TJ, Glass PS, Windsor A, *et al.* Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; **87**: 808–15

13 Doi M, Gajraj RJ, Mantazaridis H, Kenny GNC. Effects of cardiopulmonary bypass and hypothermia on electroencephalographic variables. *Anaesthesia* 1997; **52**. 1048–55

14 Stevens WE, Dolan WM, Gibbons RT, *et al* Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various age. *Anesthesiology* 1975; **42**: 197–200

15 Mapleson WW. Effect of age on MAC in humans: a meta-analysis. *Br J Anaesth* 1996; **76**: 179–85

16 Schwartz AE, Tuttle RH, Poppers PJ. Electroencephalographic burst suppression in elderly and young patients anesthetized with isoflurane. *Anesth Analg* 1989, **68**: 9–12

17 Hoffman WE, Edelman G. Comparison of isoflurane and desflurane anesthetic depth using burst suppression of the electroencephalogram in neurosurgical patients. *Anesth Analg* 1995; **81**: 811–16

18 Rampil IJ, Laster MJ. No correlation between quantitative electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. *Anesthesiology* 1992, **77**: 920–5

19 Dwyer RC, Rampil IJ, Eger EI, Bennett HL The electroencephalogram does not predict depth of isoflurane anesthesia. *Anesthesiology* 1994; **81**: 403–9

20 Olesen J. The effect of intracarotid adrenaline, noradrenaline, and angiotensin on the regional cerebral blood flow in man. *Neurology* 1972, **22**: 978–87

British Journal of Anaesthesia **84** (1). 38–42 (2000)

Behaviour of near-infrared light in the adult human head: implications for clinical near-infrared spectroscopy

A. E. R. Young[1]*, T. J. Germon[1], N. J. Barnett[2], A. R. Manara[1] and R. J. Nelson[1]

[1]*Departments of Anaesthesia and Neurosurgery, Frenchay Hospital, Frenchay, Bristol BS16 1LE, UK.*
[2]*Product Development Group, Johnson and Johnson Medical Ltd, Newport, UK*
**Corresponding author: Department of Anaesthesia, Frenchay Hospital, Frenchay, Bristol BS16 1LE, UK*

To test theoretical assumptions supporting the use of near-infrared spectroscopy (NIRS) in clinical practice, we examined the behaviour of NIR light transmission and attenuation in the human head. Sterile probes for emitting and detecting NIR light at a fixed separation of 40 mm were placed in turn on intact skin, skull, dura and cerebral cortex of 10 patients undergoing elective neurosurgery. In the first five patients, the detecting probe was moved through successive extracerebral layers with the emitter on the skin surface. In the second five patients, the process was reversed, with the emitting probe moved and the detector in the same place on the scalp. NIR intensity was measured at each tissue interface and compared with the intensity measured at the skin surface with all layers intact. Removal of bone and dura from the light path caused a significant reduction in detected intensity. The largest mean reduction in light intensity was a 14-fold decrease with removal of bone (unadjusted $P<0.0001$; paired t test). The assumptions that extracerebral tissues contribute little to attenuation of NIR light in the adult head and that most of this attenuation occurs superficially in the scalp are drawn into question by this study. We postulate that the skull and/or its interface with other layers may act as an optical 'channel', distorting the behaviour of NIR light in the human head.

Br J Anaesth 2000; **84**: 38–42

Keywords: measurement techniques, near-infrared spectroscopy; brain, near-infrared spectroscopy; surgery, neurological

Accepted for publication. July 30, 1999

Reliable non-invasive monitoring of cerebral oxygenation and metabolism is an important goal in anaesthetic and intensive care practice. On theoretical grounds, transcutaneous reflectance-mode near-infrared spectroscopy (NIRS) offers considerable promise in fulfilling these aims.

The principles which underlie the detection of changes in the concentration of oxy- and deoxyhaemoglobin by NIRS are beguilingly simple Human tissues are partly translucent to NIR light. As NIR light passes through tissue, a proportion of NIR photons are absorbed by chromophores such as oxy- and deoxyhaemoglobin. The amount of absorption depends on two predetermined factors (the wavelength of NIR light and the characteristic absorption spectra of oxy- and deoxyhaemoglobin) and two variables (the concentration of the chromophores in the tissue and the distance that the photons have to travel from their emitting source to the detector—the NIR pathlength). The greater the pathlength the greater the chance of absorption occurring and vice versa.

Thus if the pathlength of NIR light passing through a homogeneous tissue remains constant, changes in the absorption of NIR light are directly proportional to changes in the concentration of the chromophores absorbing that light. In an organ composed of heterogeneous tissues, absorption of NIR light depends on the proportion of the total pathlength which passes through each tissue compartment and the change in the concentration of chromophores in those compartments.

It has been tempting to assume that there are two principal compartments in the human head: extracerebral tissues and cerebral tissue. Much of the early work in cerebral NIR spectroscopy was conducted on the basis that the NIR pathlength in extracerebral tissues was constant and contributed relatively little to NIR light absorption, particularly if the emitting source and the detector were widely separated, thus increasing the proportion of pathlength thought to pass through cerebral tissue. These assumptions may be valid in neonates, but there is increasing evidence that they do not apply in adults.[1–4]

Schematic representations of NIR spectrometers using single or dual channel sensors often depict an elliptical light path between the emitter and detector.[5] However, the presence of discrete layers significantly affects transmission, scattering and attenuation of NIR light.[6–9] Little is known

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

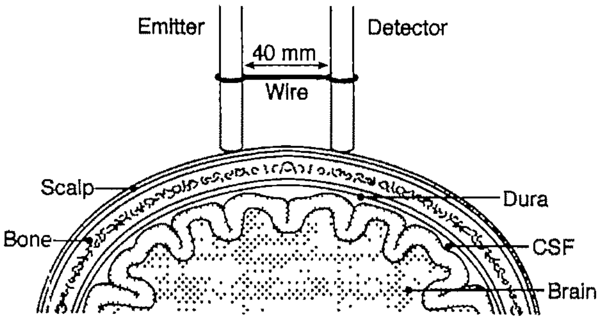


Fig 1 Apparatus for measuring baseline recording, with both the emitter and detector on the skin surface

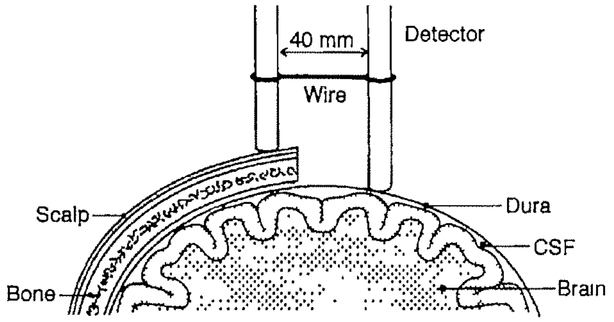


Fig 2 Apparatus with the emitter on the skin and the detector on the dura

of the transmission of NIR light at tissue interfaces *in vivo* such as those between scalp and skull, skull and dura or dura and CSF. If, as a result of these interactions, most of the NIR light path in the adult head passes through extracerebral tissues, the capacity of NIRS to detect changes in cerebral oxygenation will be reduced, particularly when perfusion and oxygenation of extracerebral tissues are unstable.

We have studied, under carefully controlled clinical conditions, whether the generally accepted models of NIR light behaviour apply in the human head, and determined the relative effects of the extracerebral tissue layers on the passage of NIR photons.

Patients and methods

We studied 10 adult patients (six females), median age 47 (range 34–65) yr, undergoing elective neurosurgical procedures involving a craniotomy or burr hole under general anaesthesia. Anaesthesia was induced with propofol, fentanyl and vecuronium and maintained with intermittent positive pressure ventilation and 1% isoflurane in nitrous oxide and oxygen. Physiological variables, including end-tidal carbon dioxide concentration, mean arterial pressure and arterial oxygen saturation, were maintained constant and within normal limits for all patients for the duration of the study. The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients.

A sterilizable probe emitting NIR light of four wavelengths (776.5, 819.0, 871.0 and 909.0 nm) and a sterilizable detecting probe (Johnson and Johnson Medical, Cerebral Redox Monitor 2001) were placed on the shaved, cleaned scalp. The two probes were kept parallel with a stainless steel wire coupling of 40 mm in length (Fig. 1). NIR intensity was recorded at the detector using a computerized data collection system. An initial baseline measurement with both probes on the scalp was recorded for 30 s. Then, with one probe remaining in the same position on the scalp, the other was placed first onto exposed skull after reflection of the scalp and periosteum, then onto intact dura after craniotomy or burr hole and finally onto the cerebral cortex after opening the dura. The separation of emitter and detector was maintained by the wire coupling at each layer (Fig. 2). A further 30-s recording of light intensity was made at the bone, dura and cerebral cortex. Haemostasis was meticulous and blood loss negligible during these phases. In the first five studies (group 1), the detecting probe was moved progressively through the anatomical layers while the emitting probe remained on the scalp. In the second five patients, the position of the probes was reversed (group 2).

For each patient, considering light of one wavelength within the NIR range (776.5 nm), a mean intensity value for the 30-s recording at each layer was obtained. The relative light intensity, using the scalp to scalp recording as the baseline measurement, was also calculated for each patient at each extracerebral layer. The ratios were log-transformed and geometric means and 95% confidence intervals (CI) were calculated for groups 1 and 2 and also for groups 1 and 2 combined. One-sample *t* tests on the log-transformed data were used to test the hypothesis that there was no change in light intensity at each layer. Paired *t* tests were used to compare the reduction of log-transformed light intensity between successive layers.

Results

Mean recordings of detected light intensity for one wavelength (776.5 nm) at each layer for each patient are shown in Table 1. The geometric mean of light intensity relative to a baseline recording (both probes on the skin) are shown for groups 1 and 2 and for all 10 subjects in Table 2. These data are also shown as averaged values for the three other wavelengths (819, 871 and 909 nm) for completeness (Table 3). The results for wavelength 776.5 nm are expressed graphically in Figure 3.

Mean light intensity relative to that recorded with both probes on the skin (baseline) for all patients was 0.485 (95% CI 0.223, 1.060) at the bone surface, 0.0338 (0.016, 0.071) at the dural surface and 0.0164 (0.005, 0.052) at the cerebral surface. Although there was an average halving of light intensity at the bone surface (with loss of the scalp) this was not statistically significant. Significant reductions were seen with loss of bone and loss of the dura. The largest geometric mean reduction was a 14-fold decrease between the bone and dural surfaces with loss of the

Table 1 NIR intensity for each patient at each layer, averaged over 30 s. Group 1=emitter maintained at the skin and the detector moved through the extracerebral layers, group 2=detector maintained at the skin with the emitter moved through the extracerebral layers

	Skin to skin	**Skin to bone**	**Skin to dura**	**Skin to cerebral cortex**
Group 1 (mean value)				
Patient No. 1	4018.3	2499.7	76.9	33.3
Patient No. 2	3615.8	793.6	36.5	2.5
Patient No. 3	2527.9	2398.9	271.6	87.1
Patient No. 4	1372.7	698.0	96.3	25.2
Patient No. 5	3445.1	5815.2	722.8	1294.3
	Skin to skin	**Bone to skin**	**Dura to skin**	**Cerebral cortex to skin**
Group 2 (mean value)				
Patient A	3419.1	6688.8	225.3	76.2
Patient B	3419.7	234.6	64.6	150.3
Patient C	6312.3	1001.0	145.4	50.6
Patient D	3422.7	3807.7	32.4	22.4
Patient E	3827.8	1063.8	90.9	75.6

Table 2 Geometric mean (95% confidence intervals) values for NIR intensity *relative* to that obtained with both probes on the skin for groups 1 and 2 and for both groups combined (total), using NIR light of wavelength 776.5nm. [1]One-sample *t* test, H_0: geometric mean=1; [2]paired *t* test

Probe position	**Group 1**	**Group 2**	**Total[1]**	**Reduction from previous layer[2]**
n	5	5	10	
Skin and bone	0.6445 (0.2517, 1.6506)	0.3661 (0.0659, 2.0329) P=0.0659	0.4858 (0.2225, 1.0604)	–
Skin and dura	0.0498 (0.0106, 0.2347)	0.0230 (0.0097, 0.0546) P<0.0001	0.0338 (0.0161, 0.0710) P=<0.0001	0.0697 (0.0337, 0.144)
Skin and cerebral cortex	0.0169 (0.0010, 0.2872)	0.0159 (0.0060, 0.0420) P<0.0001	0.0164 (0.0052, 0.0518) P=0.0494	0.48 (0.2345, 0.9978)

Table 3 Geometric mean (95% confidence intervals) values for NIR intensity *relative* to that obtained with both probes on the skin using averaged data from NIR light of wavelengths 819.0, 871.0 and 909.0 nm. [1]One-sample *t* test, H_0 geometric mean=1; [2]paired *t* test

Probe position	**Total[1]**	**Reduction from previous layer[2]**
Skin and bone	0.6414 (0.2370, 1.7356) P=0.3265	–
Skin and dura	0.0443 (0.0130, 0.1502) P=0.0005	0.0690 (0.0192, 0.2480) P=0.0017
Skin and cerebral cortex	0.0309 (0.0101, 0.0947) P=0.0002	0.6986 (0.2846, 1.7146) P=0.03763

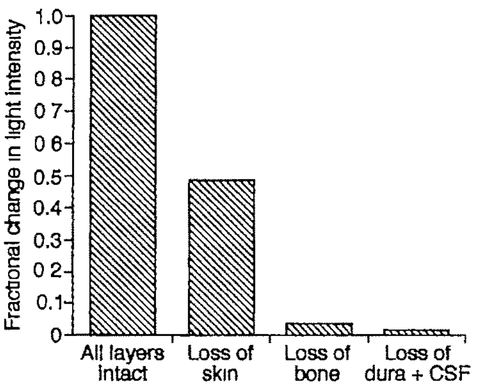


Fig 3 Mean fractional change in detected light intensity relative to baseline (with both probes on the skin) after loss of successive layers of the human head

skull (unadjusted P<0.0001; paired *t* test). There was no significant change in measured physiological variables during the study.

Discussion

In 1977, it was recognized that the differential absorption of NIR light by haemoglobin, oxyhaemoglobin and cytochrome C oxidase could be used to estimate blood flow and tissue oxygenation *in vivo*.[10] Based on these principles, cerebral NIR spectroscopy has been used for some years to monitor haemoglobin, oxyhaemoglobin and cytochrome C oxidase in neonates whose heads transmit sufficient NIR light.[11] In older children and adults, transmission NIRS is prevented by the thickness of the scalp and skull, and myelination of the brain. Reflectance-mode NIRS was developed to overcome these problems. Using this technique, NIR light is collected from the surface of the scalp ipsilateral to the light source so that the photon pathlength is significantly reduced. NIR light is thought to follow an arc whose depth is proportional to the distance between the emitter and detector and will, in theory, travel through scalp, skull, dura and finally brain before returning through the same tissue layers to be detected at the skin surface.[5]

The path of NIR light through the human head and thus the volume of cerebral tissue interrogated by reflectance-mode NIRS is unknown. The pathlength of the emitted NIR light must be known if absorption spectra are to be used to calculate absolute quantities of physiological chromophores. The mean photon pathlength may be estimated using 'time-of-flight' and other methods.[12–15] These use sophisticated technology which is not yet suitable for bedside monitoring. The effect of the extracerebral layers on the passage and pathlength of NIR light is poorly understood. There is evidence that extracerebral attenuation of NIR light influences the accuracy of all cerebral spectrometers.[1–4] It is likely that the biological and optical characteristics of the extracerebral layers vary from patient to patient and from time to time. Indeed, it is theoretically possible for NIR light to travel from the emitter to the detector without passing through cerebral tissue. It has still to be shown that the configuration of a single NIR source and one or more ipsilateral receivers is capable of detecting intracranial NIR light attenuation changes through the intact scalp, skull, dura and CSF of adult humans. In the development of clinical NIRS monitors, extracerebral attenuation of NIR light has been assumed to be small and/or predictable. In particular, bone has been thought to be translucent to NIR light.

Despite concerns about the effect of extracerebral tissues on NIR light, there have been few *in vivo* studies and most published work concerns the use of mathematical and *in vitro* models to predict the behaviour of NIR light in the adult human head.[1 2 8 16–18] In these 'phantom' models, the amount of NIR light penetrating cerebral tissue is dependent on the separation of the light emitter and detector and on the optical characteristics of the extracerebral layers.

The effect of discrete anatomical layers has been modelled. Using a simple Monte Carlo simulation of the adult head comprising two concentric spheres of differing media, Hiraoka and colleagues calculated that the pathlength of NIR light in cerebral tissue was 40–55% of the total pathlength[17]. Others have studied the effect of the CSF layer in a simple model with layers of different optical properties and in a more complex model simulating cerebral sulci.[19] Mean optical pathlength was calculated experimentally and compared with Monte Carlo predictions. The results of that study suggested that at an emitter–detector separation of 5.0 cm, 55% of the NIR light pathlength was in the scalp and skull, 20% in the CSF and, in contrast with Hiraoka's work, only 15% of the NIR pathlength was in the cerebral cortex. Because CSF has low scattering and absorption coefficients, the authors postulated that the CSF is acting as a conduit or 'channel' for the light. In their study, however, the scalp and skull were considered as one homogeneous layer. In practice, the scalp and skull have very different optical properties and thus have very different effects on NIR light behaviour and path shape. The authors stated that the fractional pathlength of scalp and skull is much greater (55%) than that of any other layer. This would support our findings; since the absorption coefficient of the skin is much greater than that of the skull, most light should therefore pass unattenuated through the skull.

In another study, cerebral blood volume (CBV) and optical pathlength were estimated in adult subjects with and without a scalp tourniquet.[20] No change was observed in NIR pathlength or CBV after arrest of scalp blood flow, confirmed by laser Doppler velocimetry. The authors concluded that scalp blood flow changes have little or no effect on NIRS measurement of cerebral haemodynamics. Cerebral blood flow (CBF) in anaesthetized patients has also been calculated using NIR probes placed first on the scalp and then on the dura.[4] CBF measured through the intact scalp was less than that measured using xenon[133] and was one-third that of NIRS measurement of CBF with probes placed on the dura. The authors concluded that underestimation was a result of extracerebral attenuation of NIR light. They suggested that 60–70% of the total optical pathlength of NIR light in the human head was through the extracerebral tissues, but they did not comment on the relative contributions of the scalp and skull or on whether the dura or CSF might have an effect.

Another recent *in vivo* NIR study demonstrated that an increase in interoptode distance from 0.7 to 5 5 cm increased the sensitivity of the monitor to cerebral attenuation changes However, at any interoptode distance, extracerebral changes were significant compared with cerebral changes, implying that extracerebral effects are important in the use of clinical NIR spectroscopy monitors, particularly at shorter interoptode distances.[21]

We studied transmission of NIR light in two distinct ways. In the first, a detecting probe was moved sequentially through the extracerebral layers of the cranium so that transmitted light intensity was sampled at each tissue interface. If the traditional model of NIR light transmission is correct, that is light travels in an arc whose depth is dependent on the separation of the emitting and detecting probes and that the extracerebral tissue layers have little effect on NIR light attenuation and path length, we would have anticipated small increases in detected optical intensity with removal of each successive extracerebral layer from the NIR light path. Alternatively, in the second part of the study, as the emitter was moved through the extracerebral layers, a greater proportion of the NIR pathlength would pass through cerebral tissue with an increased attenuation and we would have anticipated successive reductions in optical intensity detected at the skin surface.

In contrast with the anticipated findings, we observed a major decrease in detected optical intensity when bone was removed from the NIR path in both arms of the study. The changes observed when the scalp was removed from either the emitting or detecting pathway varied considerably from patient to patient and the mean reduction in intensity was not statistically significant. There was a small, statistically significant decrease in detected light intensity when the dura and CSF were removed.

We postulate that if all the extracerebral layers are intact, there is a preferential path or channel for NIR light from emitter to detector. That is, the bone or bone–dura interfaces, and to a lesser extent the dura and CSF, may be allowing 'optical channelling' of NIR photons from emitter to detector. Mathematical models have suggested that the CSF layer may act as an optical channel.[19] We do not know if the decrease in light intensity that we observed was a result of loss of the bone layer itself or loss of the bone–dura interface.

We accept that it was impossible to avoid some distortion of boundary conditions after craniotomy or burr hole. We also accept that there are minor increases in the emitter detector distance (of the order of a few millimetres) with movement of the probes from the scalp to the cerebral surface. However, the consistency and magnitude of the results in both arms of the study suggest that optical channelling may be a real phenomenon and not an artefact arising from disturbance of light transmission at optical boundaries. It is difficult to envisage another clinical experimental technique in which it is possible to maintain boundary conditions. Furthermore, if the performance of NIRS is so sensitive to boundary conditions, it will be unreliable in those conditions such as head injury, subarachnoid haemorrhage and postoperative monitoring when the boundary conditions are altered by the clinical condition itself.

We have only considered three major extracerebral layers. We have not been able to study the CSF layer independently of the other layers and it is this layer which is most likely to change with small alterations in intracranial pressure not accompanied by major changes in cerebral oxygenation. Even under carefully controlled conditions, it is clear that extracerebral tissues have a profound influence on NIR light transmission, and the behaviour of NIR light in these anatomical layers must be understood fully if NIRS is to be developed as a reliable clinical monitor.

Acknowledgements

We thank Dr John Carlin (Clinical Epidemiology and Biostatistics Unit, Royal Children's Hospital, Melbourne, Australia) for statistical advice and Dr Paul Brown (Department of Medical Physics, Frenchay Hospital) for help with data collection. Dr A E. R. Young was supported by a grant from Research and Development Directorate, NHS Executive, South and West Region.

References

1 Germon TJ, Young AER, Manara AR, Nelson RJ. Extracerebral absorption of near-infrared light influences the detection of increased cerebral oxygenation monitored by near-infrared spectroscopy. *J Neurol Neurosurg Psychiatry* 1995; **58**: 477–9

2 Harris DNF, Bailey SM. Near infrared spectroscopy in adults. *Anaesthesia* 1993; **48**: 694–6

3 Hopton P, Walsh TS, Lee A. CBF in adults using near-infrared spectroscopy: potential for bedside measurement. *Br J Anaesth* 1996; **77**: 131

4 Owen-Reece H, Elwell CE, Harkness W, et *al* Use of near-infrared spectroscopy to estimate cerebral blood flow in conscious and anaesthetised adult subjects *Br J Anaesth* 1996; **76**: 43–8

5 Cope M, Delpy DT, Reynolds EOR, Wray S, Wyatt JS, Van der Zee P. Methods of quantitating cerebral near infrared spectroscopy data. *Adv Exp Med Biol* 1988; **222**: 183–9

6 Firbank M, Schweiger M, Delpy DT. Investigation of 'light piping' through clear regions of scattering objects *Proc Soc Photooptical Instrumentation Eng* 1995; **2389**: 167–73

7 Firbank M, Arridge SR, Schweiger M, Delpy DT. An investigation of light transport through scattering bodies with non-scattering regions. *Phys Med Biol* 1996; **41**: 767–83

8 Hielscher AH, Liu H, Wang L, Tittel FK, Chance B, Jacques SL. Time resolved reflectance measurements on layered tissues with strongly varying optical properties. *Proc Soc Photooptical Instrumentation Eng* 1995; **2323**: 351–9

9 Okada E, Firbank M, Schweiger M, Arridge SR, Cope M, Delpy DT. A theoretical and experimental investigation of the effect of sulci on light propagation in brain tissue. *Proc Soc Photooptical Instrumentation Eng* 1995; **2626**: 2–8

10 Jobsis FF. Non-invasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 1977; **198**: 1264–6

11 Cope M, Delpy DT. System for long-term measurement of cerebral blood and tissue oxygenation on newborn infants by infrared transillumination. *Med Biol Eng Comput* 1988; **26**: 289–94

12 Delpy DT, Cope M, van der Zee P, Arridge S, Wray S, Wyatt J. Estimation of optical pathlength through tissue from direct time of flight measurement. *Phys Med Biol* 1988; **33**: 1433–42

13 Lakowicz JR, Berndt K. Frequency-domain measurements of photon migration in tissues. *Chem Phys Lett* 1990; **166**· 246–52

14 Cope M, Delpy DT, Wray S, Wyatt JS, Reynolds EOR. A CCD spectrometer to quantitate the concentration of chromophores in living tissue utilising the absorption peak of water at 975nm. *Adv Exp Med Biol* 1989; **248**: 33–40

15 Matcher SJ, Cope M, Delpy DT. Use of the water absorption spectrum to quantify tissue chromophore concentration changes in near infrared spectroscopy. *Phys Med Biol* 1994; **39**: 177–96

16 Hielscher AH, Liu H, Wang L, Tittel FK, Chance B, Jacques SL. Determination of blood oxygenation in the brain by time-resolved reflectance spectroscopy: influence of the skin, skull and meninges. *Proc Soc Photooptical Instrumentation Eng* 1994; **2136**: 1–27

17 Hiraoka M, Firbank M, Essenpreis M, *et al.* A Monte Carlo investigation of optical pathlength in homogenous tissue and its application to near-infrared spectroscopy. *Phys Med Biol* 1993; **38**: 1859–76

18 Okada E, Firbank M, Delpy DT. The effect of overlying tissue on the spatial sensitivity profile of near-infrared spectroscopy. *Phys Med Biol* 1995; **40**: 2093–108

19 Cui W, Kumar C, Chance B. Experimental study of migration depth for the photons measured at sample surface. *Proc Soc Photooptical Instrumentation Eng* 1991; **1431**: 180–91

20 Owen-Reece H, Elwell CE, Wyatt JS, Delpy DT. The effect of scalp ischaemia on measurement of cerebral blood volume by near-infrared spectroscopy. *Physiol Meas* 1996; **17**: 279–86

21 Germon TJ, Evans PD, Barnett NJ, Wall P, Manara AR, Nelson RJ. Cerebral near-infrared spectroscopy: emitter–detector separation must be increased. *Br J Anaesth* 1999; **82**: 831–7

British Journal of Anaesthesia 84 (1): 43–7 (2000)

Rocuronium potency and recovery characteristics during steady-state desflurane, sevoflurane, isoflurane or propofol anaesthesia†

M. Bock*, K. Klippel, B. Nitsche, A. Bach, E. Martin and J. Motsch

Department of Anaesthesiology, University of Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany

**Corresponding author*

We have studied the potency and recovery characteristics of rocuronium during 1.25 MAC of isoflurane, desflurane, sevoflurane or propofol anaesthesia in 84 patients using electromyography. Potency was determined by a cumulative bolus technique. The mean ED_{50} of rocuronium was 169 (SD 41), 126 (32), 121 (28) and 136 (25) $\mu g\ kg^{-1}$ during propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively (ns), and ED_{90} values were 358 (62), 288 (29), 289 (28) and 250 (28) $\mu g\ kg^{-1}$, respectively. The reduction in ED_{90} was statistically significant for all three inhalation anaesthetics ($P<0.05$) compared with propofol. After 120 min, the cumulative infusion rate of rocuronium to obtain twitch depression of 90–95% was 9.0 (1.9), 6.3 (1.6), 6.1 (2.0) and 6.1 (1.1) $\mu g\ kg^{-1}\ min^{-1}$ during propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively ($P<0.01$). Recovery index was 22 (13), 27 (10), 28 (13) and 26 (14) min under propofol, isoflurane, sevoflurane and desflurane anaesthesia, respectively (ns). There were no significant differences between the three potent inhalation anaesthetics in relation to potency, infusion requirements or recovery characteristics of rocuronium.

Br J Anaesth 2000; **84**: 43–7

Keywords: neuromuscular block, rocuronium; neuromuscular block, recovery; neuromuscular block, measurement of response; anaesthetics volatile, isoflurane; anaesthetics volatile, desflurane; anaesthetics volatile, sevoflurane; anaesthetics i.v., propofol

Accepted for publication: August 11, 1999

Potent inhalation anaesthetics are known to potentiate the neuromuscular blocking effects of benzylisoquinoline[1–3] and aminosteroid[4–11] neuromuscular blocking agents. Halothane,[6] enflurane[5 6] and isoflurane[5 7 8] and the new agents desflurane[8 11] and sevoflurane[9–11] have been shown to enhance the neuromuscular blocking potency of rocuronium, a newer aminosteroid neuromuscular blocking drug. To our knowledge, only one study has compared the interactions of isoflurane, desflurane and sevoflurane with a single dose of rocuronium.[11] A comparative study of the interactions of the new inhalation anaesthetics and rocuronium after continuous infusion or repeated doses of the neuromuscular blocking drug is lacking. Thus the influence of various anaesthetics on the neuromuscular effects of rocuronium during and after prolonged anaesthesia is not clear. Furthermore, to quantify the enhancement of the neuromuscular block produced by potent inhalation anaesthetics, it is important to start the investigation after adequate time has elapsed for inhalation anaesthetics to diffuse into the muscular compartment.[12]

Hence we have compared the influence of propofol, isoflurane, desflurane and sevoflurane on the potency of rocuronium during steady-state conditions after a 40-min equilibration period of the inhalation anaesthetic. In addition, the infusion rate of neuromuscular blocking drug required to maintain constant block and recovery characteristics were analysed.

Patients and methods

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 84 patients undergoing major surgery (Table 1). This prospective, randomized study was performed in close accordance to the recommendations of 'good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents'.[13] Exclusion criteria were: body weight more or less than 20% of ideal; patients younger than 18 yr; expected difficult intubation; pre-existing hepatic, renal or neuromuscular disease; allergic diathesis, pregnancy or breastfeeding; and preoperative medications known to

---

†Presented in part at the annual meeting of the German Society of Anaesthesiologists, Hamburg, Germany, April 23–26, 1997, and at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, USA, October 17–21, 1998

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Patient characteristics (mean (range) or number). No significant differences between groups

	Propofol	**Isoflurane**	**Desflurane**	**Sevoflurane**
n	21	21	21	21
Age (yr)	49.8 (21–78)	60.3 (23–81)	59.6 (37–74)	50.8 (23–77)
Sex (M/F)	7/14	11/10	11/10	9/12
Height (cm)	170 (154–181)	170 (153–199)	168 (156–181)	167 (153–181)
Weight (kg)	73.8 (49–100)	74.4 (47–105)	69.9 (42–97)	68.2 (40–100)
Duration of operation (min)	261 (160–400)	287 (200–420)	292 (135–450)	267 (170–450)
Age-adjusted 1.25 MAC of inhalation anaesthetic in N_2O (%)		0.6 (0.3–0.9)	2.8 (2.2–4.0)	1.0 (0.6–1.5)
Surgical procedure				
Major colonic resection	15	16	19	16
Upper abdominal surgery	1	0	0	1
Major urological surgery	5	5	1	3
Peripheral surgery	1	0	0	1

interact with non-depolarizing neuromuscular blocking drugs.

Study design

After oral premedication with midazolam 7.5 mg, anaesthesia was induced with fentanyl 3–7 μg kg^{-1} and propofol 2–3 mg kg^{-1}. Tracheal intubation was performed under local anaesthesia without the aid of neuromuscular blocking agents and anaesthesia was maintained according to a computer-generated randomization scheme with propofol 4–6 mg kg^{-1} h^{-1}, isoflurane, desflurane or sevoflurane (1.25 MAC of end-tidal concentration in each instance, age-adjusted) supplemented with 60% nitrous oxide in oxygen. After tracheal intubation, mechanical ventilation of the lungs was started and a neuromuscular monitor (Relaxograph; Datex, Helsinki, Finland) attached to the patient's right arm.

Neuromuscular monitoring

The arm used for neuromuscular monitoring was fixed to an arm board. The ulnar nerve was stimulated transcutaneously at the wrist via reference electrodes. Supramaximal stimuli of 0.2 ms duration in a single twitch mode at 0.1 Hz were used for potency estimation and thereafter in a TOF mode at 2 Hz every 15 s until the end of the study. The resultant force of contraction of the adductor pollicis muscle was quantified using electromyography (Relaxograph). Recovery variables were calculated using TOF ratios given on the Relaxograph readout. (This prevented discrepancies arising if the Relaxograph trace did not recover to control.)

After calibration of the Relaxograph, end-tidal P_{CO_2} was adjusted to 4.3–4.7 kPa (measured by Cicero, Draegerwerke, Lubeck, Germany). Core temperature and skin temperature over the thenar muscle were monitored and maintained at greater than 36.0°C and 32.0°C, respectively, by forced-air warming. Arterial pressure was recorded on the arm that was not used for evaluation of neuromuscular transmission. Fluids were given via a central venous line or an i.v. cannula inserted proximal to the area of nerve stimulation. Hypotension was treated with lactated Ringer's solution and small doses of vasopressor agents. During operation, fentanyl or propofol was given to maintain an adequate level of anaesthesia. Forty minutes after a 1.25 MAC end-tidal concentration of inhalation anaesthetic was reached, the Relaxograph was re-calibrated and rocuronium 0.1, 0.15 or 0.2 mg kg^{-1} was administered via the central venous line, which was not used for other medications to avoid precipitation. Maximal depression of the twitch response was recorded to calculate the dose–response curve for rocuronium. Having recorded maximal depression under stable conditions, a supplementary bolus dose of rocuronium was given so that all patients received a cumulative dose of rocuronium 0.3 mg kg^{-1}. After spontaneous recovery of the first response to 5%, a continuous infusion of rocuronium was started to maintain 90–95% neuromuscular block. The infusion rate of rocuronium needed to produce 90% continuous twitch depression was noted after 30, 60, 90 and 120 min. After cessation of the infusion, the time interval to spontaneous recovery to a TOF ratio of 0.7 was recorded.

Calculations and statistical analysis

The following variables were calculated: maximum block after the initial and supplementary dose of rocuronium (defined as maximal depression of the twitch response); time from the end of infusion to spontaneous recovery to a TOF ratio of 0.25; and time from the end of infusion to spontaneous recovery to a TOF ratio of 0.7. Recovery index was defined as the time to spontaneous recovery from a TOF ratio of 0.25 to a TOF ratio of 0.7. This was done according to clinical practice in our institution instead of TOF=0.8.[13] The dose–response relationship (mg kg^{-1}) was determined by least squares linear regression of the logarithm of each dose against a probit transformation of the initial dose and response of each patient. The effective doses to obtain 50% and 90% neuromuscular block (ED_{50} and ED_{90}, respectively) were calculated from individual dose–response curves.

Fisher's exact test, one-way ANOVA, two-tailed *t* test with Bonferroni's correction, chi-square test and two-way ANOVA were used, where appropriate, to perform statistical

Table 2 ED_{50}, ED_{90}, cumulative infusion rate of rocuronium to maintain 90–95% block and recovery index (from TOF ratio 0.25 to 0.7) during various anaesthetic regimens. $^*P<0.05$, $^{**}P<0.01$ between propofol and inhalation anaesthesia groups

	Propofol	**Isoflurane**	**Desflurane**	**Sevoflurane**
ED_{50} ($\mu g\ kg^{-1}$)	169 (41)	126 (32)	136 (25)	121 (28)
ED_{90} ($\mu g\ kg^{-1}$)	358 (62)*	288 (29)	250 (28)	289 (28)
Infusion rate at 120 min ($\mu g\ kg^{-1}\ min^{-1}$)	9.0 (1.9)**	6.3 (1.6)	6.1 (1.1)	6.1 (2.0)
Recovery index (min)	22 (13)	27 (10)	26 (14)	28 (13)

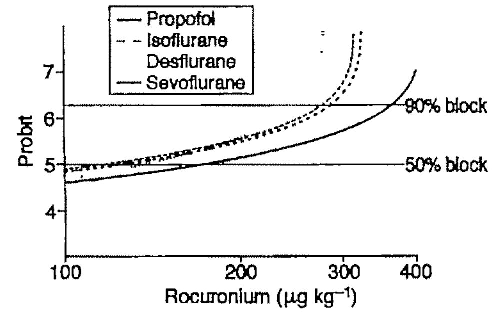


Fig 1 Dose–response curves for rocuronium during propofol, isoflurane, desflurane, sevoflurane and propofol anaesthesia. During inhalation anaesthesia, the dose–response relationship was shifted to the left compared with propofol.

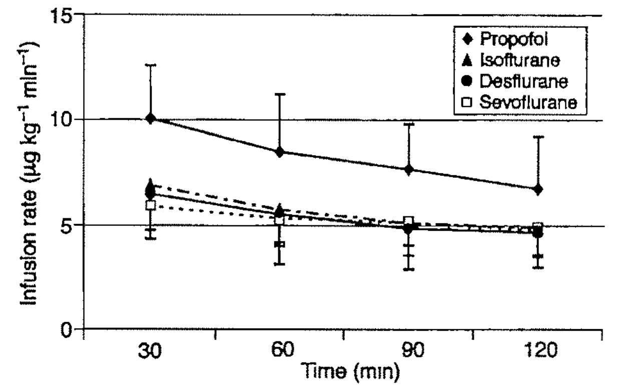


Fig 2 Mean (SD) infusion rate of rocuronium required to maintain 90–95% neuromuscular block. Significant difference ($P<0.01$) between propofol anaesthesia compared with each inhalation anaesthetic.

analyses of physical characteristics and pharmacodynamic data. Data are given as mean (SD or range).

Results

Patient characteristics, type and duration of surgery, and end-tidal concentrations of the inhalation anaesthetic are given in Table 1. There were no significant differences between groups. During the study, an end-tidal concentration of 1.25 MAC of the inhalation anaesthetic was maintained in all patients.

The mean ED_{50} of rocuronium was 169 (SD 41) $\mu g\ kg^{-1}$ during propofol, 126 (32) $\mu g\ kg^{-1}$ during isoflurane, 121 (28) $\mu g\ kg^{-1}$ during sevoflurane and 136 (25) $\mu g\ kg^{-1}$ during desflurane anaesthesia (Table 2). The reduction in ED_{50} of rocuronium by the inhalation anaesthetics was not statistically significant. In contrast, the ED_{90} of rocuronium was 358 (62) $\mu g\ kg^{-1}$ under propofol, 288 (29) $\mu g\ kg^{-1}$ under isoflurane, 289 (28) $\mu g\ kg^{-1}$ under sevoflurane and 250 (28) $\mu g\ kg^{-1}$ under desflurane anaesthesia (Table 2). This reduction was statistically significant for all inhalation anaesthetics compared with propofol anaesthesia ($P<0.05$). There were no significant differences between the potency of the inhalation anaesthetics. The groups receiving potent inhalation anaesthetics showed comparable slopes of the dose–response curves, and the curves were shifted to the left (Fig. 1).

After 120 min, the cumulative infusion rate of rocuronium to obtain twitch depression of 90–95% was 9.0 (1.9) $\mu g\ kg^{-1}\ min^{-1}$ during propofol, 6.3 (1.6) $\mu g\ kg^{-1}\ min^{-1}$ during isoflurane, 6.1 (1.1) $\mu g\ kg^{-1}\ min^{-1}$ during desflurane and 6.1 (2.0) $\mu g\ kg^{-1}\ min^{-1}$ during sevoflurane anaesthesia (see Table 2). During propofol anaesthesia, the cumulative infusion rate was significantly greater compared with the inhalation anaesthetics ($P<0.01$). There were no significant differences between the potent inhalation anaesthetics. Figure 2 shows the infusion rates of rocuronium required to maintain 90–95% block at 30, 60, 90 and 120 min. Patients receiving potent inhalation anaesthetics had lower requirements for rocuronium compared with those receiving propofol ($P<0.01$). There were no significant differences between the inhalation anaesthetics. In all groups, the infusion rates were reduced to avoid accumulation of the neuromuscular blocking agent. Recovery index was 22 (13) min under propofol, 27 (10) min under isoflurane, 28 (13) min under sevoflurane and 26 (14) min under desflurane anaesthesia (Table 2). There were no significant differences between groups. Inter-individual variability of the neuromuscular response was lowest among patients receiving isoflurane anaesthesia.

Discussion

During steady state conditions, we found that there was a marked interaction between the neuromuscular blocking effects of rocuronium and isoflurane, desflurane and sevoflurane, resulting in a leftward shift of the dose–response curve (Fig. 1). To maintain 90–95% neuromuscular block, the infusion rate of rocuronium was reduced by 30–40% during isoflurane, desflurane and sevoflurane anaesthesia compared with propofol.

After the age-adjusted end-tidal concentration of the inhalation anaesthetic was reached, another period of 40 min was allowed to elapse before the first dose of rocuronium was given. As tracheal intubation is usually performed after only a short period of anaesthesia, it may be of theoretical importance to wait for equilibration of the muscular compartment with the inhalation agent before estimating the dose–response relationship. However, the duration of action of a neuromuscular blocking drug and the amount needed for maintenance during long operations are affected by the type and duration of anaesthesia. Particularly for determination of infusion rate, it is important to study the interactions between neuromuscular blocking drugs and anaesthetics at pre-set stable concentrations of inhalation agent.[12] It is generally accepted that 40 min is sufficient for equilibration of the muscular compartment with volatile anaesthetics which have a high blood-gas coefficient.[12] In clinical practice, intermediate-acting neuromuscular blocking agents are often given repeatedly and not as a single bolus. In our opinion, it is also important to estimate the recovery variables of these drugs after complete equilibration of the muscular compartment with the potent inhalation anaesthetic has been allowed to occur. This opinion has been confirmed by two reports on recovery from aminosteroid neuromuscular blocking drugs: in one, time to 25% recovery after a single dose of vecuronium was prolonged when the dose was given 60 or 120 min after the beginning of anaesthesia with sevoflurane.[14] In contrast, a 30-min period of stabilization did not prolong the time to 25% recovery. In the second study, after rocuronium 0.6 mg kg^{-1}, recovery indices were prolonged when 0.8 MAC of isoflurane, desflurane or sevoflurane was administered compared with 0.4 MAC.[15]

Compared with previous studies,[6 8–11] we found no clinically important differences between the ED_{50} and ED_{90} of rocuronium under various inhalation anaesthetics. In all studies, the potency of rocuronium was found to be increased by 25–40% under inhalation anaesthesia compared with propofol. The amount of potentiation of the neuromuscular blocking effect of rocuronium seems to be inversely related to the MAC of each anaesthetic. This effect has been demonstrated for the older inhalation anaesthetics halothane, enflurane and isoflurane.[12] For isoflurane, desflurane and sevoflurane, our results are in accordance with Wulf and co-workers.[11] Other groups, however, found lower values for the ED_{50}, but not for the ED_{95}, of rocuronium under isoflurane than under desflurane anaesthesia.[8] Thus the amount of potentiation of the neuromuscular blocking effect of rocuronium under desflurane anaesthesia remains somewhat unclear as does the degree of potentiation of vecuronium under desflurane anaesthesia. Desflurane or isoflurane 1 MAC was shown to have similar effects on the potency of vecuronium.[16] In contrast, others observed greater potentiation of the neuromuscular effects of vecuronium under desflurane than under isoflurane anaesthesia.[17] Halothane, enflurane and isoflurane were shown to augment the neuromuscular block of vecuronium, and an inverse relation to their analgesic and hypnotic potency was observed.[4] After a wash-in period of 40 min, the potencies of vecuronium, pancuronium and atracurium were augmented by isoflurane and sevoflurane to the same degree.[18]

In clinical practice, the influence of the potent inhalation anaesthetics on the infusion rate at which complete neuromuscular block is obtained is important. Our results are in agreement with Shanks, Fragen and Ling,[5] who compared the infusion rate of rocuronium under balanced, enflurane and isoflurane anaesthesia. Under inhalation anaesthesia, the infusion rate was reduced by 40%. As in our study, the choice of inhalation anaesthetic had no effect on the total dose of rocuronium required to maintain constant neuromuscular block. In another study, isoflurane reduced the infusion requirements of rocuronium by 35–40% compared with various i.v. anaesthetics.[7] The infusion rates of vecuronium also have to be reduced when inhalation anaesthetics are used for maintenance of anaesthesia.[19]

The time to spontaneous recovery from a TOF ratio of 0.25 to 0.7 was only slightly, but not significantly, affected by the presence of potent inhalation anaesthetics in our study. Provided that the infusion rate of rocuronium is adjusted to produce 90% block, the time to complete recovery during desflurane, sevoflurane and isoflurane anaesthesia is only slightly prolonged. Compared with isoflurane anaesthesia, the recovery variables were also slightly, but not significantly, prolonged during desflurane anaesthesia in another study in which a single dose of rocuronium 0.6 mg kg^{-1} was given.[8] In a recent study, the recovery index after a single dose of rocuronium was prolonged during sevoflurane anaesthesia compared with isoflurane or propofol anaesthesia.[10] This may be a result in part of lack of equilibration of the muscle compartment as only 10 min of anaesthesia had been allowed to pass before the neuromuscular blocking agent was given. On the other hand, inter-individual variability was found to be much higher during sevoflurane anaesthesia in that study. In contrast, pancuronium, vecuronium and atracurium showed comparable prolongation of recovery after sevoflurane and isoflurane.[18] After continuous infusion of rocuronium for 120 min, recovery also tended to be prolonged when anaesthesia with enflurane or isoflurane was compared with barbiturate–nitrous oxide–opioid anaesthesia.[5] In another study, the recovery index after neuromuscular block produced by cisatracurium was prolonged during desflurane and sevoflurane anaesthesia compared with propofol or isoflurane anaesthesia.[3] Thus recovery during inhalation anaesthesia may be related inversely to analgesic and hypnotic potency, or to blood solubility. This hypothesis, however, needs to be proved in further studies.

Acknowledgements

We thank Dr H Bauer for statistical support. This work was part of the MD thesis of B. N., University of Heidelberg, Faculty of Medicine.

References

1 Kansanaho M, Olkkola KT. Quantifying the effect of isoflurane on mivacurium infusion requirements. *Anesth Analg* 1996; **51**: 133–6

2. Meretoja OA, Wirtavuori K, Taivainen T, Olkkola KT. Time course of potentiation of mivacurium by halothane and isoflurane in children. *Br J Anaesth* 1996; **76**: 235–8
3. Wulf H, Kahl M, Ledowski T. Augmentation of the neuromuscular blocking effects of cisatracurium during desflurane, sevoflurane, isoflurane or total i.v. anaesthesia. *Br J Anaesth* 1998; **80**: 308–12
4. Rupp SM, Miller RD, Gencarelli PJ Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984, **60**: 102–5
5. Shanks CA, Fragen RJ, Ling D. Continuous intravenous infusion of rocuronium (ORG 9426) in patients receiving balanced, enflurane, or isoflurane anesthesia. *Anesthesiology* 1993; **78**: 649–51
6. Oris B, Crul JF, Vandermeersch E, Van Aken H, Van Egmond J, Sabbe MB. Muscle paralysis by rocuronium during halothane, enflurane, and total intravenous anesthesia. *Anesth Analg* 1993; **77**. 570–3
7. Olkkola KT, Tammisto T. Quantifying the interaction of rocuronium (Org 9426) with etomidate, fentanyl, midazolam, propofol, thiopental, and isoflurane using closed-loop feedback control of rocuronium infusion. *Anesth Analg* 1994; **78**: 691–6
8. Kumar N, Mirakhur RK, Symington MJJ, McCarthy GJ. Potency and time course of action of rocuronium during desflurane and isoflurane anaesthesia. *Br J Anaesth* 1996; **77**: 488–91
9. Xue FS, Liao X, Tong SY, Liu JH, An G, Luo LK. Dose–response and time-course of the effect of rocuronium bromide during sevoflurane anaesthesia. *Anaesthesia* 1998; **53**: 25–30
10. Lowry DW, Mirakhur RK, McCarthy GJ, Carroll MT, McCourt KC. Neuromuscular effects of rocuronium during sevoflurane, isoflurane, and intravenous anesthesia. *Anesth Analg* 1998, **87**: 936–40
11. Wulf H, Ledowski T, Linstedt U, Proppe D, Sitzlack D Neuromuscular blocking effects of rocuronium during desflurane, isoflurane, and sevoflurane anaesthesia. *Can J Anaesth* 1998; **45** 526–32
12. Agoston S. Interactions of volatile anaesthetics with rocuronium bromide in perspective. *Eur J Anaesthesiol* 1994; **11** (Suppl. 9): 107–11
13. Viby-Mogensen J, Engbaek J, Eriksson LI, *et al* Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. *Acta Anaesthesiol Scand* 1996; **40**: 59–74
14. Kumagai M, Ahmed AAK, Ozaki M, Kondo I, Amaki Y. Effect of sevoflurane exposure time on neuromuscular blocking action of vecuronium *Anesthesiology* 1998; **89** (Suppl). A973
15. Schmidt J, Albrecht DM. Neuromuscular blocking effects of rocuronium under different concentrations of desflurane, sevoflurane and isoflurane compared to intravenous anesthesia. *Anesthesiology* 1998; **89** (Suppl): A999
16. Ghouri AF, White PF. Comparative effects of desflurane and isoflurane on vecuronium induced neuromuscular blockade *J Clin Anesth* 1992; **4**: 34–8
17. Wright PMC, Hart P, Lau M, *et al* Magnitude and time course of vecuronium potentiation by desflurane versus isoflurane. *Anesthesiology* 1995; **82**: 404–11
18. Vanlinthout LEH, Booij LHDJ, Van Egmond J, Robertson EN Effect of isoflurane and sevoflurane on the magnitude and time course of neuromuscular block produced by vecuronium, pancuronium and atracurium. *Br J Anaesth* 1996; **76** 389–95
19. Cannon JE, Fahey MR, Castagnoli KP, *et al* Continuous infusion of vecuronium: The effect of anesthetic agents. *Anesthesiology* 1987, **67**: 503–6

British Journal of Anaesthesia 84 (1): 48–58 (2000)

Single-dose ketorolac and pethidine in acute postoperative pain: systematic review with meta-analysis

L. A. Smith, D. Carroll, J. E. Edwards, R. A. Moore and H. J. McQuay*

Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford Radcliffe Hospital, The Churchill, Headington, Oxford OX3 7LJ, UK

**Corresponding author: Pain Research, University of Oxford, Oxford Radcliffe Hospital, The Churchill, Headington, Oxford OX3 7LJ, UK*

For a systematic review of postoperative analgesic efficacy and adverse effects of single doses, injected or oral, of pethidine and ketorolac compared with placebo, we sought published randomized studies in moderate to severe postoperative pain. Information on summed pain intensity or pain relief outcomes over 4–6 h was extracted and converted to dichotomous information to produce the number of patients with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat (NNT) for one patient to achieve at least 50% pain relief. Minor and major adverse effect data were extracted and summarized. For pethidine 100 mg i.m., eight randomized, controlled studies met the inclusion criteria, with 203 patients given pethidine and 161 placebo. The NNT to produce at least 50% pain relief was 2.9 (95% confidence interval 2.3–3.9). At this dose, pethidine produced significantly more drowsiness and dizziness than placebo, with numbers-needed-to-harm (NNH) of 2.9 (2.2–4.4) and 7.2 (4.8–14), respectively. For ketorolac, 14 reports met the inclusion criteria (six i.m. and eight oral). Most i.m. information (176 patients) was available for the 30 mg dose, which had an NNT of 3.4 (2.5–4.9). Most oral information was available for the 10 mg dose, which had an NNT of 2.6 (2.3–3.1). Oral ketorolac 10 mg was consistently at least as effective as ketorolac 30 mg i.m. Only with oral ketorolac 10 mg were there significantly more adverse effects than with placebo, with an NNH for any adverse effect of 7.3 (4.7–17).

Br J Anaesth 2000; **84**: 48–58

Keywords: analgesics non-opioid, ketorolac; analgesics opioid, pethidine; pain, postoperative; analgesia, audit; research, analgesia; non-steroidal anti-inflammatory drugs

Accepted for publication: August 13, 1999

Pethidine is a commonly used postoperative opioid analgesic, and ketorolac is a newer non-steroidal anti-inflammatory drug (NSAID), licensed for short-term use in the management of moderate to severe postoperative pain. Injectable NSAID are a popular alternative to injected opioids in acute pain, even though we lack evidence that NSAID are more effective by injection than by mouth.[1] How effective and safe are they, and how do they compare with opioids used in this pain setting?

It is important to be able to compare the relative efficacy and safety of analgesics to make informed decisions on which analgesic to prescribe. A very large randomized study making direct comparisons between analgesics would provide data on their relative efficacy and safety. Such studies do not exist. The published randomized trials of direct comparisons between analgesics are too small, and hence lack power for their estimates of relative efficacy and safety to be credible.

An alternative method of estimating relative efficacy is by indirect comparisons of each analgesic with placebo. By pooling data from individual studies of an analgesic *vs* placebo with similar pain settings, pain outcome measures and study design, we can estimate the number-needed-to-treat (NNT) for at least 50% pain relief. By using these same criteria for each analgesic and by using 50% pain relief as a common descriptor of analgesic efficacy, it is possible to produce a rank order of NNT values that describes clinically relevant pain relief.

The league table of analgesic efficacy[2] shows the relative NNT values of oral analgesics used for acute postoperative pain. The studies used to produce the NNT values were all single-dose, postoperative, randomized and double-blind. All patients had moderate to severe pain before being treated. Standard pain outcomes and measures of pain were used. Internal validity of the league table is shown by the dose–response rankings within it. To date, the only NNT available for an i.m. analgesic is for morphine 10 mg,[3] and the league table needs more i.m. data to be clinically useful

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Details of i m pethidine *vs* placebo single-dose studies

Author	Condition and no. of patients	Design, study duration and follow-up	Treatment groups	Outcome measures	Analgesic outcome results (pethidine *vs* placebo)	Withdrawals and exclusions	Adverse effects	Comment	Quality score
Bloomfield *et al*, 1983 Study 1[35]	Post-partum episiotomy $n=20$, age >16 yr	RCT, DB, identical ampoules, single dose, parallel group Assessed at 0, 0 5, 1, 1 5 h then hourly up to 6 h Severe stitch pain	1 Pethidine 100 mg i m, $n=10$ 2 Placebo, $n=10$ 3 Metkephamid 70 mg i m, $n=10$	1 PI 4-point standard scale (0–3) 2 PR 4-point non standard scale (0–3) 3 Patient global 10-point non-standard scale (0–10)	1 6 h SPID pethidine 15 5, placebo 9 0	None	Number of patients reporting AEs pethidine 6/10, placebo 2/10	Pethidine 100 mg, more effective than metkephamid 70 mg and placebo	4
Bloomfield *et al*, 1983 Study 2[35]	Post-partum episiotomy $n=20$, age >16 yr	RCT, DB, identical ampoules, single dose, parallel group Assessed at 0, 0 5, 1, 1 5 h then hourly up to 6 h Severe stitch pain	1 Pethidine 100 mg i m, $n=10$ 2 Placebo, $n=9$ 3 Metkephamid 140 mg i m, $n=10$	1 PI 4-point standard scale (0–3) 2 PR 4-point non-standard scale (0–3) 3 Patient global 10-point non-standard scale (0–10)	1 6 h SPID pethidine 13 0, placebo 5 6	One patient took analgesia within 4 h pre-study dose 12/59 received rescue analgesia	Number of patients reporting AEs pethidine 8/19, placebo 3/9	Metkephamid 140 mg more effective than pethidine 100 mg, both more effective than placebo	4
Calimlin *et al*, 1982[36]	Post-operative not specified	RCT, DB, single dose, parallel group Assessed at 0, 0 5, 1, 1 5 h then hourly up to 6 h At least moderate baseline pain	1 Pethidine 100 mg i m, $n=11$ 2 Placebo, $n=11$ 3 Metkephamid 70 mg, $n=10$	1 PI 5-point non-standard scale (0–4) 2 PR 5-point standard scale (0–4) 3 VASPI 100 mm 4 Patient global 5-point scale (1–5)	1 6 h TOTPAR pethidine 9 5, placebo 1 3 2 Global rating pethidine 2 5, placebo 1 3	Two placebo patients remedicated in first hour of study and excluded	Number of patients reporting AEs pethidine 36 4%, placebo 33 3%	Both active treatment groups similar and more effective than placebo	3
DeAndrade *et al*, 1996	Major orthopaedic surgery $n=198$, age 18–87 yr	RCT, DB, multi-centre study, single and multiple doses, attempts to blind with use of amber syringes, parallel groups Assessed at 0, 0 5, 1 h then hourly up to 6 h At least moderate baseline pain	1 Pethidine 100 mg i m, $n=82$ 2 Placebo, $n=35$ 3 Ketorolac 60 mg i m, $n=81$	1 PI 5-point non-standard scale (0–4) 2 PR 5-point standard scale (0–4) 3 VASPI 100 mm 4 Patient global non-standard 5-point scale (0–4)	1 6 h TOTPAR pethidine 9 7, placebo 1 7 2 6 h SPID pethidine 4 3, placebo –0 1	44 patients excluded because of study violations and insufficient sample	No AE data for single dose	Both active treatments similar and more effective than placebo	5

Table 1 *Continued*

Author	Condition and no. of patients	Design, study duration and follow-up	Treatment groups	Outcome measures	Analgesic outcome results (pethidine *vs* placebo)	Withdrawals and exclusions	Adverse effects	Comment	Quality score
Folsland *et al*, 1990	Major abdominal surgery $n=129$, Age 17–82 yr	RCT, DB, identical ampoules, single dose, parallel group Assessed at 0, 0 5, 1 h then hourly up to 8 h Moderate to severe baseline pain	1 Pethidine 100 mg i m., $n=27$ 2 Placebo, $n=32$ 3 Ketorolac 10 mg i m, $n=31$ 4 Ketorolac 30 mg i m, $n=29$	1 VASPI 100 mm 2 VASPR 100 mm 3 Patient global 5-point standard scale (0–4)	1 6 h VASTOTPAR pethidine 301, placebo 122 85 2 6 h VASPID pethidine 191 7, placebo 77 6 3 Global rating pethidine 5/27 very good or excellent, placebo 1/32 very good or excellent	One withdrawal because of nausea (pethidine), 2 pethidine withdrawals because of study violations, 3 pethidine, 1 placebo excluded from efficacy analysis because of incomplete data	Number of patients reporting AEs pethidine 6/32, placebo 1/32	All active treatments better than placebo Pethidine 100 mg similar to ketorolac 30 mg	4
Sherline, 1983	Post-Caesarean pain, $n=21$, age 18–40 yr	RCT, DB, identical ampoules, single dose, Assessed at 0 5, 1, 1 5, 2 h and then hourly up to 6 h Moderate to severe baseline pain	1 Pethidine 100 mg i m., $n=11$ 2 Placebo, $n=10$ 3 Picenadol 25 mg i m, $n=11$	1 PI 5-point non-standard scale (0–4) 2 PR 5-point standard scale (0–4)	1 6 h TOTPAR pethidine 19 7, placebo 5 7	One placebo excluded because of unreliable responses	Number of patients reporting AEs pethidine 11/11, placebo 4/10	Both active treatments better than placebo Pethidine 100 mg similar to picenadol 25 mg	4
Sunshine *et al*, 1984	Post-Caesarean section or major gynaecological surgery, $n=94$ age 18–75 yr	RCT, DB, single parallel group Assessed at 0, 0 5, 1 h then hourly until 4 h Moderate to severe baseline pain	1 Pethidine 50 mg i m, $n=30$ 2 Pethidine 100 mg i m, $n=32$ 3 Placebo, $n=32$ 4 Flunixin 20, 40 and 80 mg i m, all $n=32$	1 PI 4-point standard scale (0–3) 2 PR DNS scale 3 Patient global, DNS scale	1 4 h SPID pethidine 50 mg 3 64, pethidine 100 mg 4 69, placebo 2 77	DNS	Number of patients reporting AEs pethidine 50 mg 5/30, pethidine 100 mg 8/32, placebo 2/32	All active treatments better than placebo	2
Wang and Robinson, 1993	Various post-operative procedures, $n=62$, age 21–70 yr	RCT, DB, identical ampoules, single parallel group Assessed at 0 5, 1, 1 5, 2 h then hourly until 6 h Moderate to severe baseline pain	1 Pethidine 50 mg i m, $n=21$ 2 Pethidine 100 mg, i m., $n=20$ 3 Placebo $n=21$ 4 Doxcipomine 200 mg i m, $n=21$ 5 Doxcipomine 400 mg i m, $n=20$	1 PI 5-point non-standard scale (0–4) 2 PR 5-point standard scale (0–4)	1 6 h TOTPAR pethidine 50 mg 9 1, pethidine 100 mg 10 3, placebo 5 4 2 6 h SPID pethidine 50 mg 6.2, pethidine 100 mg 6 7, placebo 3 3	Two patients withdrew from doxcipomine	AE reported for pethidine 100 mg only	Pethidine 100 mg similar to doxcipomine 400 mg, all active groups better than placebo	4

in the postoperative setting. We set out to provide more i.m. NNT data, examining pethidine and ketorolac. Efficacy is only part of the equation, for both prescribers and patients, and we also compared and contrasted the adverse effect profiles of the three i.m. analgesics morphine, pethidine and ketorolac.

Methods

Randomized controlled studies of ketorolac or pethidine *vs* placebo in postoperative pain were sought. Studies of epidural, intrathecal or i.v. routes using patient-controlled analgesia (PCA) were not included. Several different search strategies were used to identify eligible reports from MEDLINE (1966 to July 1998), EMBASE (1980–1998), the Cochrane Library (1998, issue 2) and the Oxford pain relief database (1950–1994).[4] Broad free text searches with no restriction to language were undertaken using the terms 'ketorolac', 'Toradol', 'pethidine', 'postoperat*', 'operat*', 'postsurg*', 'surg*', 'dental', 'molar', 'extract*', 'random*', 'double blind', 'dummy', 'study', 'trial', 'analgesi*', 'pain' and seven brand names (including Meperidine and Demerol). Reference lists of retrieved reports were searched for additional studies. Abstracts and review articles were not considered. Roche Products Ltd (UK) were contacted for ketorolac reports. Authors of articles were not contacted for unpublished reports or additional information from published reports.

Inclusion criteria and data extraction

The criteria for inclusion in the meta-analyses were: full journal publication of randomized controlled trials which included single-dose treatment groups of i.v., i.m. or oral pethidine and placebo, or ketorolac and placebo; double-blind design, baseline postoperative pain of moderate to severe intensity or visual analogue pain intensity of at least 30 mm[5]; patients of more than 15 yr of age; and standard pain scales. These scales were the four-point pain intensity scale (none, mild, moderate, severe), the five-point pain relief scale (none, slight, moderate, good, complete) or their visual analogue (VAS) equivalents. Study duration had to be 4–6 h, and there had to be sufficient data to allow calculation of total pain relief (TOTPAR) or summed pain intensity difference (SPID) or their visual analogue equivalents (VASTOTPAR and VASSPID).

Each report which could possibly be described as a randomized controlled study was scored independently for quality by two of the authors (pethidine L. A. S. and D. C.; ketorolac D. C. and H. J. M.) using a three-item, 1–5 score, quality scale.[6] Reports which were described as 'randomized' were given one point, and another point if the method of randomization was described and adequate (such as a table of random numbers). Randomization was assumed when stated as such in the report. One point was given when the study was described as 'double-blind'. When the method of double-blinding was described and adequate (e.g. tablets of identical colour, shape and taste), another point was given. Finally, reports which described the number and reasons for withdrawals were given 1 point. Thus the maximum score of an included randomized controlled study was 5 and the minimum 1. Authors met to agree consensus. Data extracted from each study were: type of surgery; study treatment groups; number of patients treated; study duration; dose of pethidine or ketorolac and route of administration; and mean or derived 4–6 h TOTPAR, SPID, VASTOTPAR or VASSPID. Where available, information on the type, incidence and severity of adverse effects, including study withdrawals, was also extracted.

Statistical analyses

The proportion of patients in each treatment group who achieved at least 50% of the maximum possible total pain relief (maxTOTPAR) was calculated using verified equations.[7–9] These proportions were then converted into the number of patients achieving at least 50% maxTOTPAR by multiplying by the total number of patients in the treatment group. Information on the number of patients with at least 50% maxTOTPAR for active and placebo was then used to calculate relative benefit and NNT. Information on adverse effects was used, where possible, to calculate the relative risk and NNH.

Relative benefit and risk estimates were calculated with 95% confidence intervals using a fixed effects model.[10] NNT and NNH with confidence intervals were calculated by the method of Cook and Sackett.[11] When relative benefit or risk was statistically significant (95% confidence interval did not include 1), the respective NNT or NNH values are given in the text and tables, and the relative benefits and risks are shown only in the tables. When relative benefit or risk was not statistically significant, it is given in the text and tables, and respective NNT or NNH values were not calculated. Calculations were performed using Excel v 5.0 on a Power Macintosh 8500/150.

All of the data that we were able to extract are shown in Tables 1–6. In principle, however, it is preferable to make conclusions from substantial data,[12] and to emphasize that substantial data are more credible, we have emphasized the rows in the tables where we had at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment.

Results

Pethidine

We identified 24 placebo-controlled pethidine studies but only eight met our inclusion criteria. The citations and reasons for excluding the 16 studies are available at http://www.jr2.ox.ac.uk/Bandolier/painres/pethketo/pethketo.html.

Eight randomized studies generating 10 pethidine *vs* placebo comparisons fulfilled our inclusion criteria; 254

Table 2 Relative benefit and number-needed-to-treat (NNT) for studies of i.m. pethidine compared with placebo nc=Not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

Pethidine dose (mg)	No. of comparisons	No. of patients with at least 50% pain relief		Relative benefit (95% CI)	NNT (95% CI)
		With pethidine	With placebo		
50	2	19/51	12/53	1 7 (0 9–3.0)	nc
100	**8**	**109/203**	**30/161**	**3.2 (2.3–4.6)**	**2.9 (2.3–3.9)**

Table 3 Relative risk and number-needed-to-harm (NNH) for studies of i.m. analgesics compared with placebo. nc=Not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

Drug and dose	Adverse effects	No. of studies	No. of patients reporting adverse effects		Relative risk (95% CI)	NNH (95% CI)
			With active	With placebo		
Pethidine 100 mg	Withdrawals because of adverse effect	3	9/65	4/77	2.2 (0 8–6 4)	nc
	Any adverse effect	**7**	**136/201**	**41/139**	**1.7 (1.4–3.0)**	**2.6 (2.1–3.6)**
	Drowsiness/somnolence	**5**	**103/158**	**29/96**	**1.6 (1.2–2.0)**	**2.9 (2.2–4.4)**
	Dizziness/light-headedness	**5**	**27/158**	**3.96**	**6.6 (2.1–21)**	**7.2 (4.8–14)**
	Nausea/vomiting	**4**	**39/147**	**13/86**	**1.4 (0.8–2.3)**	**nc**
Morphine 10 mg	Withdrawals because of adverse effect	**6**	**3/195**	**2/192**	**1.2 (0.3–4.5)**	**nc**
	Any adverse effect	**15**	**108/320**	**68/295**	**1.5 (1.1–2.0)**	**9.1 (5.6–28)**
	Drowsiness/somnolence	3	49/94	15/67	2.7 (1.7–4 3)	3.4 (2.3–6 4)
	Dizziness/light-headedness	3	43/80	7/79	5.7 (2.8–12)	2.2 (1.8–3.1)
	Nausea/vomiting	**6**	**41/166**	**12.164**	**3.3 (1.8–6.0)**	**5.9 (4.0–11)**
Ketorolac 10 mg	Withdrawals because of adverse effect	2	0/70	0/74		nc
	Any adverse effect	2	14/70	7/74	2 1 (0 9–5.0)	nc
	Drowsiness/somnolence	1	6/38	5/41	1.3 (0 4–3 9)	nc
	Dizziness/light-headedness			None reported		
	Nausea/vomiting	2	7/70	2/74	3.7 (0 8–17)	nc
Ketorolac 30 mg	Withdrawals because of adverse effect	**3**	**1/119**	**0/119**		**nc**
	Any adverse effect	**3**	**19/119**	**16/119**	**1.2 (0.6–2.2)**	**nc**
	Drowsiness/somnolence	2	9/81	10/82	0.9 (0 4–2 1)	nc
	Dizziness/light-headedness	1	0/41	5/41	0 1 (0 01–1.6)	nc
	Nausea/vomiting	3	**19/119**	**15/119**	**1.3 (0.7–2.4)**	**nc**

patients were given pethidine 50 or 100 mg i.m. and 214 placebo. No studies of oral or i.v. pethidine at any dose met our inclusion criteria. The studies investigated pain relief predominantly after orthopaedic, general or gynaecological surgery. Pain outcomes were over 6 h except for one study which was over 4 h[13]. One report scored 5 points on the quality scale, five reports scored 4, one scored 3 and one report scored 2. Further study characteristics are included in Table 1.

Efficacy

I.m. pethidine vs placebo. In the two comparisons of pethidine 50 mg *vs* placebo, 51 patients received pethidine and 53 placebo. There was no significant benefit of pethidine over placebo (Table 2).

There were eight comparisons of pethidine 100 mg vs placebo (Table 1); 203 patients received pethidine and 161 placebo. For a single dose of pethidine 100 mg, the proportion of patients with at least 50% pain relief was 43–100% (mean 54%) and 0–70% (mean 19%) for placebo (Fig. 1). Pethidine 100 mg was statistically superior to placebo, with an NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain of 2.9 (2.3–3.9) (Table 2).

Adverse effects

Only for pethidine 100 mg i.m. *vs* placebo was sufficient information available for analysis of adverse effects. Thirteen patients withdrew from the studies because of adverse effects (Table 3). Nine patients who received pethidine withdrew; nausea was the most frequently reported adverse effect causing premature study termination.[14 15] Four patients on placebo withdrew, one because of severe drowsiness, and three for reasons that were not specified.[14 16]

Seven of the eight randomized studies comparing a single dose of pethidine 100 mg with placebo reported adverse effect information. One study provided data only for those patients who received pethidine and not for those who received placebo.[17] Sixty-eight percent (136 of 201) of patients who received pethidine reported an adverse effect compared with 30% (41 of 139) of patients who received placebo. For a single dose of pethidine 100 mg i.m. compared with placebo, the NNH to report any adverse effect was 2.6 (2.1–3.6) (Table 3).

Six of the seven randomized studies reported the frequency and type of individual adverse effects. The adverse effects most frequently reported were drowsiness or somnolence, dizziness or light-headedness and nausea or vomiting.

Table 4 Details of ketorolac *vs* placebo single-dose studies

Author	**Condition and no. of patients**	**Design, study, duration and follow-up**	**Treatment groups**	**Outcome measures**	**Analgesic outcome results (ketorolac *vs* placebo)**	**Withdrawals and exclusions**	**Adverse effects**	**Quality score**
Injected								
Estenne *et al*, 1988	Various major surgery (gynaecological, urological, abdominal), *n*=160 (159 included in analysis), age 18–85 yr	RCT, DB, not identical yellow injectable preparations. Single dose, parallel group. Assessed at 0, 0.5, 1 h then hourly up to 8 h. At least moderate baseline pain, 1 ml injections into vastus laterus	1. Ketorolac 10 mg i.m., *n*=38 2. Ketorolac 30 mg i.m., *n*=39 3. Placebo *n*=41 4. Pentazocine 30 mg i.m., *n*=41	1. PI 5-point (0–4) 2. PR 5-point (0–4) 3. Patient and investigator global rating 5-point (1–5) 4. Would patient take tablets again?	1. 6 h SPID K10 9.2 *vs* K30 10.7 *vs* P 6.7 2. 6 h TOTPAR K10 13.8 *vs* K30 17.7 *vs* P 10.2 3. Patient global scores >50% K10 23/38 *vs* K30 33/39 *vs* P 15/41	Mean time to re-medication (h) K10 7.5 *vs* K30 7.9 *vs* P 7.0	No. of patients reporting AEs K10 8/38 *vs* K30 9/40 *vs* P 6/41 Study withdrawals because of AEs: not reported	2
Folsland *et al*, 1990	Major abdominal surgery, *n*=129 (119 included in efficacy analysis), age 17–82 yr	RCT, DB, not identical yellow injectable preparations. Single dose, parallel group. Single investigator assessments at 0, 30 min, 1 h then hourly up to 8 h. At least moderate baseline pain. 1 ml injections into vastus laterus	1. Ketorolac 10 mg i.m., *n*=32 2. Ketorolac 30 mg i.m., *n*=32 (*n*=29 analysed) 3. Placebo *n*=33 (*n*=32 analysed) 4. Pethidine 100 mg i.m., *n*=32 (*n*=27 analysed)	1. VASPI 100 mm 2. VASPR 100 mm 3. Investigator and patient global rating 5-point (0–4)	1. 6 h VASSPID K10 114.8 *vs* K30 174.6 *vs* P 60.9 2. 6 h VASTOTPAR K10 178.9 *vs* K30 259.5 *vs* P 102.5 3. 6 h patient global rating K10 15/32 *vs* K30 18/29 *vs* P 9/32	No. remedication with inadequate relief K10 29 (91%) K30 21 (72%) P 30 (94%)	No. of patients reporting AEs K10 6/32 *vs* K30 2/32 *vs* P30 1/32 Study withdrawals because of AEs K30 1/29 K10 0/32 *vs* P 0/32	3
Parke *et al*, 1995	Major orthopaedic, *n*=113 (112 analysed), age 17–82 yr	RCT, single dose, double-blind, not identical yellow injectable preparations parallel group. Assessments (by patient observed by investigator) at 0, then every 2 min up to 10 min, every 5 min up to 45 min, then 1, 2, 3, 4, 5, 6 h. At least moderate baseline pain	1. Ketorolac 30 mg/1 ml i.m., *n*=38 2. Ketorolac 10 mg/1 ml i.v., *n*=38 3. Placebo *n*=37	1. Verbal ordinal score P1 0–100 2. PI (4-point) (0–3) 3. Patient global rating end of treatment 5-point (0–4)	1. Global rating good–excellent KIV 13/37 *vs* KIM 9/38 *vs* P 2/37	% remedicated at 6 h KIV 78% *vs* P 95%	No serious adverse effects reported	5
DeAndrade *et al*, 1996	Major orthopaedic surgery, *n*=244 (200 included in analysis), age 18–87 yr	RCT, DB, multicentre (7 sites), single and multiple dose as required. Not identical yellow injectable preparations. Assessments at 0, 30 min, 1 h then hourly up to 6 h. At least moderate baseline pain within 48 h of surgery	1. Ketorolac 60 mg i.m. (multiple dose 30 mg) *n*=97 (81 analysed) 2. Pethidine 100 mg i.m., *n*=97 (82 analysed)	1. PI 5-point (0–4) 2. PR 5-point (1–5) 3. Patient global rating 5-point (1–5)	1. 6 h SPID K30 5.9 *vs* P –0.1 2. 6 h TOTPAR: K30 12.2 *vs* P 1.7	44 excluded for variety of reasons 200/244 in final analysis. Patients remedicated within 6 h K60 35/81 43%) *vs* P 35/35 (100%)	No AE data for single dose	5
Laveneziana *et al*, 1996	Hernia repair, *n*=125 (124 included in analysis), age 18–72 yr	RCT, single dose, double-dummy. Not identical yellow injectable preparations parallel group. Assessments (by patient observed by investigator) at 0, 15, 30 min, 1, 2, 3, 4, 5, 6 h. At least moderate baseline pain	1. Ketorolac 30 mg i.m., *n*=41 2. Placebo *n*=41 3. Ibuprofen arginine 400 mg orally *n*=42	1. VASPI 100 mm 2. Patient global rating 5-point (0–4)	1. NSD between active treatments and placebo, except subgroup analysis 2. No. of patients rating treatment as at least good K 22/40 *vs* P 14/41	No. remedication with inadequate relief K 12/41 *vs* P 17/41	No adverse effects reported	4
Pagnoni *et al*, 1996	Caesarean section, *n*=92, age 18 yr +	RCT, single dose, parallel group, single centre, double-dummy. Not identical yellow injectable preparations. Assessments (by patient observed by investigator) at 0, 15, 30 min, 1, 2, 3, 4, 5, 6 h. Baseline pain at least 60 mm VASPI	1. Ketorolac 30 mg i.m., *n*=30 2. Placebo *n*=32 3. Ibuprofen arginine 400 mg orally *n*=30	1. VASPI 100 mm 2. Patient global rating 5-point (0–4)	1. Derive VASSPID from Fig. 3B or 2 2. No. of patients rating treatment as at least good K 16/30 *vs* P 4/32	No. remedication with inadequate relief K 13/30 *vs* P 21/32	No adverse effects reported	4
Oral								
Forbes *et al*, 1990	Impacted lower third molars, *n*=128, age 16–41 yr	RCT, single and multiple dose DB, double-dummy, parallel group, single nurse observer, assessments at 0, 30 min, 1 h then hourly for 6 h. At least moderate baseline pain	1. Ketorolac 10 mg orally *n*=37 2. Placebo *n*=32 3. Acetaminophen 600 mg + codeine 60 mg orally *n*=27 4. Aspirin 650 mg orally *n*=32	1. PI (4-point) 0–4 SPID 2. PR (5-point) TOTPAR 3. VASPI (0–99 VASSPID 4. Patient global (5-point) 0–4	1. 6 h SPID K 5.65 *vs* P 0.25 2. 6 h TOTPAR K 12.41 vs P 2.91 3. Hours of 50% pain relief. K 3.07 *vs* P 0.72 4. Patient global rating K 2.81 *vs* P 0.72	161/162 available at 1 week follow-up. Results based on data from 128 for efficacy and 142 for safety. No. of patients re-medication K 2.81 *vs* P 27/32	No. of patients reporting AEs K 10/39 *vs* P 5/34 Study withdrawals for single dose not given	5

Table 4 *Continued*

Author	**Condition and no. of patients**	**Design, study, duration and follow-up**	**Treatment groups**	**Outcome measures**	**Analgesic outcome results (ketorolac *vs* placebo)**	**Withdrawals and exclusions**	**Adverse effects**	**Quality score**
Forbes *et al.*, 1990	Impacted lower third molars, *n*=206, age 16–48 yr	RCT, single and multiple dose, multi-centre, DB, double-dummy, parallel group, single nurse observer, assessments at 0, 30 min, 1 h then hourly for 6 h At least moderate baseline pain	1. Ketorolac 10 mg orally *n*=31 2 Ketorolac 20 mg orally *n*=35 3 Placebo *n*=34 4 Ibuprofen 400 mg orally *n*=32 5 Acetaminophen 600 mg orally *n*=36 6 Acetaminophen 600 mg + codeine 60 mg orally *n*=38	1. PI (4-point) 0–3 SPID 2 PR (5-point) 0–4 TOTPAR 3 VASPI 0–99 VASSPID 4. Patient global rating (5-point) 0–4	1 6 h SPID K10 5 84 *vs* K20 5 69 *vs* P 0 59 2 6 h TOTPAR K10 11 84 *vs* K20 12 57 *vs* P 1 88 3 Hours of 50% pain relief K10 3 25 *vs* K20 3 83 *vs* P 0 29 4 Patient global rating K10 2 39 *vs* K20 2 56 *vs* P 0 56	265/269 available at 1 week follow-up 206 evaluable for efficacy, 244 evaluable for safety No of patients remedication K10 18/31 *vs* K20 19/35 *vs* P 33/34	No of patients reporting AEs K10 5/39 *vs* K20 8/43 *vs* P 0/38 Study withdrawals for single dose not given	5
Fricke *et al*, 1993	Third molar extraction, *n*=207, age 16 yr +	RCT, DB, single (multiple dose) Assessments at 0, 15, 30, 60, 90, 120, 180, 240, 300, 360 min At least baseline pain	1 Ketorolac 10 mg orally *n*=71 2 Placebo *n*=69 3 Hydrocodone 10 mg + paracetamol 1 g orally *n*=69	1 VASPI 0–100 2 CATPI (0–4) 3 Overall patient rating end of treatment 5-point (0–4)	1 6 h SPID (means only) 2 6 h TOTPAR 3. 6 h global	Patients receiving rescue analgesia 6 h K 11/30 P 11/30	No major AEs reported Minor AEs K 43 events in 23/71 patients P 30 events in 20/69 patients	3
Maslanka *et al.*, 1994	Orthopaedic surgery, *n*=176, age 19–87 yr	RCT, single dose, DB, double-dummy, parallel group, assessments at 0, 30 min, 1 h then hourly for 6 h At least moderate baseline pain	1 Ketorolac 10 mg orally *n*=50 2 Placebo *n*=25 3 Morphine 10 mg i m., *n*=50 4 Morphine 5 mg i m , *n*=50	1 PI (4-point) 0–4 SPID 2 PR (5-point) 0–4 TOTPAR 3. VASPI 0–99 VASSPID	1 6 h SPID K 6 9 *vs* P 2 42 2 6 h VASSPID K 197 4 *vs* P 77 33 3 6 h TOTPAR K 12 6 *vs* P 5.0	1/176 patients excluded from analysis 105 completed 6 h study: K 33/50 *vs* P 7/25	No of patients reporting AEs: K 18/50 *vs* P 5/25 5 study withdrawals for AEs: K 3/50 *vs* P 3/25	4
Reines *et al*, 1994	Orthopaedic surgery, *n*=242, age 18–95 yr	RCT, multicentre, DB, single dose, parallel group Assessments at 0, 30, min, 1 h then hourly intervals for up to 6 h Follow-up at 1 week (some treatments taken at home) At least moderate baseline pain	1 Ketorolac 10 mg orally *n*=76 2 Placebo *n*=73 3 Oxycodone + acetaminophen 325 mg orally *n*=69	1 PI (5-point) 0–4 SPID 2 PR (5-point) 0–4 TOTPAR 3. Patient global rating (5-point) 0–4	1. 6 h SPID derive from Fig 1 2 6 h TOTPAR P 3 1 *vs* K 7 6	242 patients enrolled, 218 included in analysis	No of patients reporting AEs. P 22 (30%) *vs* K 40 (52%)	3
Nørholt *et al*, 1995	Third molar extraction *n*=300, age 17–40 yr	RCT, multicentre, DB, but not double-dummy, single dose, parallel group Assessments at 0, 0 5, 1 h then hourly intervals for up to 8 h Follow-up at 1 week At least moderate baseline pain	1 Ketorolac 10 mg orally *n*=46 2 Placebo *n*=48 3 Lornoxicam 4 mg orally *n*=43 4. Lornoxicam 8 mg orally *n*=45 5 Lornoxicam 16 mg orally *n*=48 6 Lornoxicam 48 mg orally *n*=43	1 PI (5-point) 0–4 2 PR (5-point) 0–4 TOTPAR 3. Patient global rating (5-point) 1–5	1 6 h TOTPAR 3.7 *vs* K 14 1 2 Patient global of good or excellent P 4/48 *vs* K 25/46	278/300 took part, 22 excluded from analysis Results for 266 patients	26 patients reported 37 AEs No treatment related study withdrawals Patients reporting AEs P 7/48 *vs* K	3
White *et al*, 1997	Ambulatory athroscopic and laparascopic tubal ligation, *n*=252 (10 excluded protocol violations), adult females	RCT, multicentre, DB, single dose, parallel group Assessment at 0, 30 min, 1 h then hourly intervals for up to 6 h Stratification by operation type At least moderate baseline pain Escape analgesia permitted at 1 h	1 Ketorolac 10 mg orally *n*=82 2 Placebo *n*=82 3 Hydrocodone 7 5 mg + acetaminophen 750 mg orally *n*=87	1 PI (4-point) 0–3 SPID 2 PR (5-point) 0–4 TOTPAR 3 Patient global rating (5-point) 1–5	1. 6 h SPID split by op type 2. 6 h TOTPAR split by op type 3 Global rating 6 h good + K 57/87, P 59/83	10 excluded study violations Patients in study at 6 h K 3/83 P 5/87	No AEs reported	3

Table 5 Details of pooled analyses of different routes and doses of ketorolac. RB=Relative benefit, NNT=number-needed-to-treat; nc=not calculated because relative benefit not statistically significant. Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

Dose	Route	No. of studies	At least 50% pain relief on ketorolac	At least 50% pain relief on placebo	RB (95% CI)	NNT (95% CI)
10 mg	I.m.	2	33/69	22/73	1.6 (1.1–2.4)	5.7 (3.0–53)
30 mg	**I.m.**	**5**	**93/176**	**42/183**	**2.3 (1.8–3.1)**	**3.4 (2.5–4.9)**
60 mg	I.m.	1	45/81	0/35	40 (2.5–626)	1.8 (1.5–2.3)
10 mg	I.v.	1	13/37	2/37	6.5 (1.6–27)	3.4 (2.1–7.9)
5 mg	Oral	1	21/30	17/30	1.2 (0.8–1.8)	nc
10 mg	**Oral**	**8**	**205/410**	**43/380**	**4.3 (3.2–5.8)**	**2.6 (2.3–3.1)**
20 mg	Oral	1	20/35	0/34	39 (2.5–632)	1.8 (1.4–2.5)

Table 6 Analgesia with single doses of i.m. analgesics for postoperative pain Bold type indicates at least three studies using the same dose and route of administration, and ideally at least 100 patients given the active treatment

Drug and dose	No. of studies	No. of patients given drug	NNT (95% CI)
Pethidine 100 mg	**8**	**203**	**2.9 (2.3–3.9)**
Morphine 10 mg	**15**	**486**	**2.9 (2.6–3.6)**
Ketorolac 10 mg	2	69	5.7 (3.0–53)
Ketorolac 30 mg	**5**	**176**	**3.4 (2.5–4.9)**

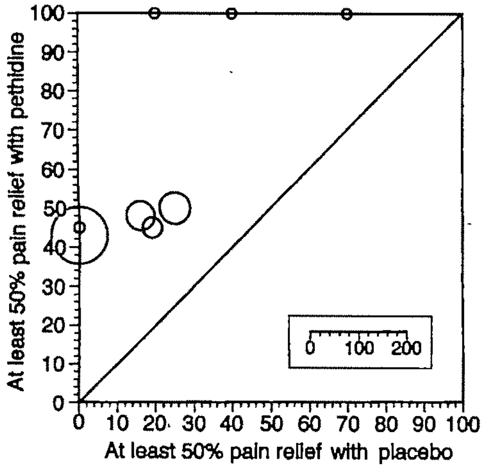


Fig 1 Proportion of patients in each study achieving at least 50% pain relief. Pain relief was over 4–6 h for pethidine 100 mg i.m. in randomized double-blind studies in patients with pain of at least moderate intensity. Point size is linearly proportional to the total number of patients in each study.

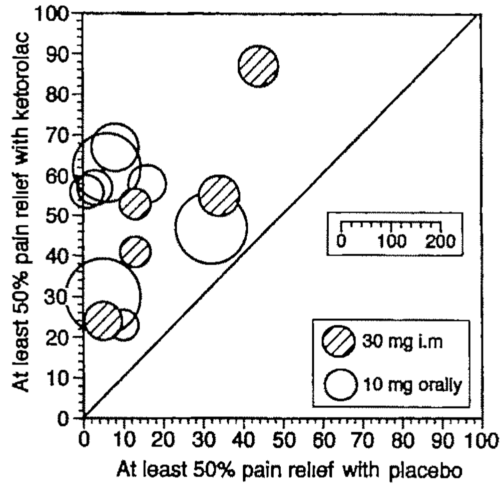


Fig 2 Proportion of patients in each study achieving at least 50% pain relief Pain relief was over 4–6 h for ketorolac 30 mg i.m. and 10 mg orally in randomized double-blind studies in patients with pain of at least moderate intensity. Point size is linearly proportional to the total number of patients in each study.

Pethidine produced significantly higher incidences than placebo of drowsiness or somnolence (NNH 2.9 (2.2–4.4)) and dizziness or light-headedness (7.2 (4.8–14)). There was no significant difference in the incidence of nausea or vomiting between pethidine and placebo (relative risk 1.4 (0.8–2.3)) (Table 3).

Ketorolac

Fourteen reports met the inclusion criteria. There were six studies of i.m. ketorolac *vs* placebo and eight of oral ketorolac *vs* placebo (Table 4). Quality scores were 3 or greater in all but one report. Four reports scored 5 points, four scored 4, five scored 3 and one scored 2 points. One report[18] compared ketorolac 10 mg i.v. (38 patients) with placebo (Table 5). Details of the 55 studies excluded from the review are available at: http://www.jr2.ox.ac.uk/Bandolier/painres/pethketo/pethketo.html.

Efficacy

I.m. ketorolac vs placebo. Six reports[14 15 18–21] contained eight comparisons of i.m. ketorolac with placebo, five at 30 mg, two at 10 mg and one at 60 mg. There was a total of 326 patients given i.m. ketorolac and 291 given placebo.

The proportion of patients obtaining at least 50% pain relief was 5–44% for placebo (mean 22%), 22–66% for ketorolac 10 mg i.m., 24–87% for ketorolac 30 mg i.m. (mean 53%) (Fig. 2, Table 5) and 56% for ketorolac 60 mg i.m. The NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain for the two reports of ketorolac 10 mg i.m. was 5.7 (3.0–53), and with increasing dose the NNT decreased (Table 5). For ketorolac 30 mg i.m., studied in five trials and with the most information, the NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain was 3.4 (2.5–4.9).

Oral ketorolac vs placebo. Eight reports[22–29] involved a total of 410 patients given ketorolac 10 mg orally and 380 given placebo. One report[22] also compared ketorolac 5 mg orally (30 patients) with placebo and another[24] compared ketorolac 20 mg orally (35 patients) with placebo.

The proportion of patients obtaining at least 50% pain relief was 1–32% for placebo (mean 10%), 70% for ketorolac 5 mg orally, 23–67% for ketorolac 10 mg orally (mean 50%; Fig. 2) and 57% for ketorolac 20 mg orally. The NNT for at least 50% pain relief over 4–6 h in patients with moderate or severe pain for eight reports of ketorolac 10 mg orally was 2.6 (2.3–3.1), and with increasing dose the NNT decreased (Table 5).

Adverse effects

I.m. ketorolac. One patient who received ketorolac 30 mg i.m. withdrew because of dry mouth[15]; with a 10-mg dose, no patient withdrew because of adverse effects (Table 3). At both 10 mg and 30 mg, adverse effects were not considered clinically serious and were described as mild or moderate.

Three studies reported adverse effects after ketorolac 30 mg i.m. (19 of 119 patients; 16%) compared with placebo (16 of 119 patients; 13%).[18–20] There was no significant difference between ketorolac and placebo when data were pooled for all reported adverse effects (relative risk 1.2 (0.7–2.2)). Two studies reported adverse effects of ketorolac 10 mg i.m. (14 of 70 patients; 20%) compared with placebo (seven of 74 patients; 9%).[15 19] There was no significant difference between ketorolac and placebo when data were pooled for all reported adverse effects (relative risk 2.1 (0.9–5.0)).

The adverse effects reported most often were drowsiness or somnolence, dizziness or light-headedness, nausea or vomiting and dry mouth (Table 3), but there were no significant differences between ketorolac and placebo.

Oral ketorolac 10 mg. Four patients withdrew from studies because of adverse effects; three after ketorolac and one after placebo. Two patients who received ketorolac reported nausea and one reported severe headache.[25–27] One patient who received placebo withdrew with nausea.[26]

Five studies provided information on the total number of patients who had reported adverse effects.[23 24 26–28] Thirty-one percent (79 of 250) of patients who received ketorolac reported adverse effects compared with 18% (39/218) who received placebo. With a single dose of ketorolac compared with placebo, the NNH for a patient to report any adverse effect was 7.3 (4.7–17).

Six studies reported the frequency and type of individual adverse effects.[23–28] The adverse effects reported most often were drowsiness or somnolence, dizziness or light-headedness, nausea or vomiting and dry mouth (Table 4), but there were no significant differences between ketorolac and placebo.

Discussion

It was surprising that, despite rigorous searching, there were so few placebo-controlled studies in which pethidine had been given by i.v., i.m. or oral routes, and for both pethidine and ketorolac, so few studies using standard validated methods to test single-dose analgesic efficacy. The reasons are in part historic, because pethidine is an old drug and was not used as often as morphine as a comparator in studies, and partly novelty. Many investigations of ketorolac used outcomes such as opioid-sparing effect rather than categorical or visual analogue scales. The quality of the studies included was high for both pethidine and ketorolac.

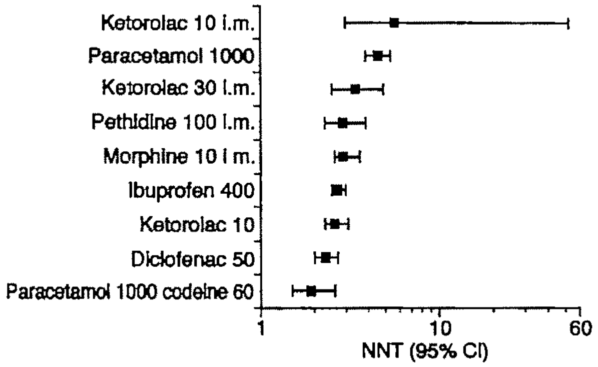


Fig 3 Numbers-needed-to-treat (NNT) (95% confidence intervals) for at least 50% pain relief over 4–6 h in patients with moderate or severe postoperative pain. All doses are oral unless labelled i.m. Data for pethidine and ketorolac from this article, for morphine from McQuay, Carroll and Moore RA[3] and for other drugs from McQuay and Moore.[2]

Efficacy

Only for injected morphine do we have sufficient data to be confident in our estimates.[12] Table 6 summarizes the analgesic efficacy for the two i.m. opioids pethidine and morphine,[3] and the i.m. NSAID ketorolac. There is clearly little difference in efficacy between i.m. morphine 10 mg, pethidine 100 mg and ketorolac 30 mg. A theoretical limitation of this NNT method summarizing efficacy over 4–6 h is that it does not tell us if there are differences between the drugs for time to peak effect or duration beyond 6 h. Clearly, overall the areas under the pain relief vs time curves for these drugs at these doses were comparable. Figure 3 shows the NNT values for these i.m. doses and, for comparison, the NNT values for oral ketorolac, other oral NSAID and paracetamol, alone and in combination with codeine 60 mg.

Ketorolac 10 mg orally and 30 mg i.m. had NNT values (2.6 and 3.4, respectively, compared with placebo) which were similar to aspirin 650 mg[30] (4.4), paracetamol 1000 mg[31] (3.6), ibuprofen 400 mg[32] (2.7) and diclofenac 50 mg[32] (2.3). The comparisons were with placebo, in patients with moderate or severe pain after surgery, and all used the outcome of at least 50% pain relief over 4–6 h.

We showed that, because confidence intervals of ketorolac 10 mg orally and 30 mg i.m. overlapped, they could not be distinguished in their analgesic efficacy. This is consistent with a review of NSAID which failed to demonstrate any benefit of injected over oral administration.[1] What was interesting in this review was that oral ketorolac appeared consistently to be at least as potent as i.m. ketorolac (Fig. 3). The reasons for this are not immediately obvious. Use of analgesics by injection is expected to lead to faster increases in blood concentrations and hence faster onset of action. Oral administration is expected to lead to reduced bioavailability, and slower and lower blood concentrations than the same drug and dose given by injection. In addition to the kinetic difference between oral and injected routes, there is also a mechanistic difference between opioids and NSAID. Opioids act via receptors, NSAID by inhibiting enzymes. For ketorolac, the kinetic distinction does not seem to apply. In younger and older volunteers, ketorolac 10 mg orally resulted in more rapid maximal blood concentrations than ketorolac 30 mg i.m..[33] Nor was there any difference in dose-corrected areas under the concentration–time curve, indicating no substantial presystemic elimination with oral administration.

Another possible reason for the apparent effectiveness of oral ketorolac may be that it was given to patients with less severe pain. This is also unlikely. All studies used pain of at least moderate severity as an inclusion criterion. The studies all had a placebo-treated group. If there was any major difference in initial pain intensity between patients who were given oral or injected preparations, then it might be reflected in lower rates of placebo response. This did not occur (Fig. 2). The range of patients achieving at least 50% pain relief with placebo was 5–44% in the injected ketorolac studies (mean 22%) and 1–32% in the oral ketorolac studies (mean 14%).

The most likely explanation is that there is no real difference between oral and i.m. ketorolac over the dose ranges studied. This is supported by a wider review of injected and oral NSAID.[1] To demonstrate a small difference of statistical rather than clinical significance would require many more patients than found in these studies.[12] The practice point is that oral administration is very often simpler than i.m.[2]

Adverse effects

Table 3 summarizes the adverse effect data for the two i.m. opioids pethidine and morphine, and i.m. ketorolac. The similarity between the incidence of minor adverse effects of morphine 10 mg and pethidine 100 mg at these equianalgesic doses is to be expected. For the i.m. NSAID ketorolac, there were no significant differences from placebo in the incidence of minor adverse effects at 10 or 30 mg. This is slightly surprising because for oral ketorolac 10 mg compared with placebo, we found a number-needed-to-harm of 7.3 (4.7–17) for one patient to report an adverse effect. Indeed, with aspirin, ibuprofen and paracetamol, there was increased reporting of any adverse effect compared with placebo.[30 34] The explanation for the greater incidence of adverse effects with 10 mg orally compared with 30 mg i.m. may be that there were too few patients in the i.m. ketorolac analysis to produce accurate estimates of the incidence of adverse effects.

The clinical conclusion is that opioids carry a small but finite risk of serious adverse effects such as respiratory depression, and a greater risk of minor adverse effects than single-dose injected or oral NSAID. Conversely, NSAID carry a risk of renal problems after operation. Analgesia from the injected doses, opioid or NSAID, was equivalent to that achieved with oral NSAID. Higher doses of opioid can produce greater analgesia.[3] For patients who cannot swallow, the choice is injected opioid vs injected NSAID. Our information suggests that in patients who can swallow, and in whom NSAID are not contra-indicated, oral NSAID are as effective as injected NSAID, and provide analgesia equivalent to that from conventional doses of injected opioid.

Acknowledgements

This study was supported by grants from NHS R&D Health Technology Evaluation programmes (No 93/31/4 and No. 94/11/4), European Union Biomed 2 BMH4 CT95 0172, BBSRC and SKB Consumer Healthcare, and from Pain Research Funds.

References

1 Tramèr MR, Williams JE, Carroll D, Wiffen PJ, Moore RA, McQuay HJ. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* 1998; **42**: 71–9

2 McQuay HJ, Moore RA. An *Evidence-Based Resource* for *Pain Relief.* Oxford: Oxford University Press, 1998

3 McQuay HJ, Carroll D, Moore RA. Injected morphine in postoperative pain: a quantitative systematic review. *J Pain Symptom Manage* 1999; **17**: 164–74

4 Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996; **66**: 239–46

5 Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain* 1997; **72**: 95–7

6 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12

7 Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics. *Pain* 1996; **66**: 229–37

8 Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Verification from independent data. *Pain* 1997; **69**: 127–30

9 Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: Use of pain intensity and visual analogue scales. *Pain* 1997; **69**: 311–15

10 Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *BMJ* 1986; **292**: 746–50

11 Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995; **310**: 452–4

12 Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything–large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998; **78**: 209–16

13 Sunshine A, Zighelboim I, Olson N, De Castro A, Laska E. Analgesic efficacy of intramuscular flunixin meglumine compared to meperidine: a preliminary report. *NIDA Res Monogr* 1984; **55**: 145–50

14 DeAndrade JR, Maslanka M, Reines HD, *et al.* Ketorolac versus meperidine for pain relief after orthopaedic surgery. *Clin Orthop Relat Res* 1996; **325**: 302–12

15 Folsland B, Skulberg A, Halvorsen P, Helgesen KG. Placebo controlled comparison of single intramuscular doses of ketorolac tromethamine and pethidine for post operative analgesia. *J Int Med Res* 1990; **18**: 305–14

16 Sherline DM. Picenadol (LY 150720) compared with meperidine and placebo for relief of post-cesarean section pain: A randomized double-blind study. *Am J Obstet Gynecol* 1983; **147**: 404–6

17 Wang RI, Robinson N. Further efficacy evaluation of doxpicomine for postoperative pain. *J Clin Pharmacol* 1983; **23**: 44–7

18 Parke TJ, Millett S, Old S, Goodwin APL, Rice ASC. Ketorolac for early postoperative analgesia. *J Clin Anesth* 1995; **7**: 465–9

19 Estenne B, Julien M, Charleux H, Arsac M, Arvis G, Loygue J. Comparison of ketorolac, pentazocine, and placebo in treating postoperative pain. *Curr Ther Res* 1988; **43**: 1173–82

20 Laveneziana D, Riva A, Bonazzi M, Cipolla M, Migliavacca S. Comparative efficacy of oral ibuprofen arginine and intramuscular ketorolac in patients with postoperative pain. *Clin Drug Invest* 1996; **11**: 8–14

21 Pagnoni B, Vignali M, Colella S, Monopoli R, Tiengo N. Comparative efficacy of oral ibuprofen arginine and intramuscular ketorolac in patients with postcaesarean section pain. *Clin Drug Invest* 1996; **11**: 15–21

22 Honig WJ, Van Ochten J. A multiple-dose comparison of ketorolac tromethamine with diflunisal and placebo in postmeniscectomy pain. *J Clin Pharmacol* 1986; **26**: 700–5

23 Forbes JA, Butterworth GA, Burchfield WH, Beaver WT. Evaluation of ketorolac, aspirin, and an acetaminophen–codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990; **10**: 77–93S

24 Forbes J, Kehm C, Grodin C, Beaver W. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophen codeine combination in postoperative oral surgery pain. *Pharmacotherapy* 1990; **10**: 94–105S

25 Fricke J, Halladay SC, Bynum L, Francisco CA. Pain relief after dental impaction surgery using ketorolac, hydrocodone plus acetaminophen, or placebo. *Clin Ther* 1993; **15**. 2–11

26 Maslanka MA, de Andrade JR, Maneatis T, Bynum L, DiGiorgio E. Comparison of oral ketorolac, intramuscular morphine, and placebo for treatment of pain after orthopedic surgery. *South Med J* 1994; **87**: 506–13

27 Reines HD, Adams D, Hawkes T. Evaluation of oral ketorolac oxycodone plus acetaminophen, and placebo for pain relief after orthopaedic surgery. *Curr Ther Res* 1994; **55**: 615–24

28 Nørholt SE, Sindet Pedersen S, Bugge C, Branebjerg PE, Ersboll BK, Bastian HL. A randomized, double-blind, placebo-controlled, dose–response study of the analgesic effect of lornoxicam after surgical removal of mandibular third molars. *J Clin Pharmacol* 1995; **35**: 606–14

29 White PF, Joshi GP, Carpenter RL, Fragen RJ. Comparison of oral ketorolac and hydrocodone–acetaminophen for analgesia after ambulatory surgery: arthroscopy versus laparoscopic tubal ligation. *Anesth Analg* 1997; **85**: 37–43

30 Edwards JE, Oldman A, Smith L, *et al.* Oral aspirin in postoperative pain: a quantitative systematic review. *Pain* 1999; **81**: 289–97

31 Moore A, Collins S, Carroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review. *Pain* 1997; **70**: 193–201

32 Collins SL, Moore RA, McQuay HJ, Wiffen PJ. Oral ibuprofen and diclofenac in postoperative pain: a quantitative systematic review. *Eur J Pain* 1998; **2**: 285–91

33 Buckley MMT, Brogden RN. Ketorolac–a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. *Drugs* 1990; **39**: 86–109

34 Edwards JE, McQuay HJ, Moore RA, Collins SL. Guidelines for reporting adverse effects in clinical trials should be improved–lessons from acute pain *J Pain Symptom Manage* (in press)

35 Bloomfield SS, Barden TP, Mitchell J. Metkephamid and meperidine analgesia after episiotomy. *Clin Pharmacol Ther* 1983; **34**: 240–7

36 Calimlim JF, Wardell WM, Sriwatanakul K, Lasagna L, Cox C. Analgesic efficacy of parenteral metkephamid acetate in treatment of postoperative pain. *Lancet* 1982; **1**: 1374–5

British Journal of Anaesthesia 84 (1): 59–62 (2000)

Hyperbaric bupivacaine for spinal anaesthesia in 7–18 yr old children: comparison of bupivacaine 5 mg ml^{-1} in 0.9% and 8% glucose solutions

H. Kokki* and H. Hendolin

Department of Anaesthesiology and Intensive Care, Kuopio University Hospital,
PO Box 1777, FIN-70211 Kuopio, Finland
**Corresponding author*

We have compared two hyperbaric bupivacaine solutions for spinal anaesthesia in 7–18-yr-old school-aged children in a double-blind, randomized, parallel group, prospective study. Children were premedicated with diazepam orally. Half of the patients were sedated with either midazolam or thiopental. After lumbar puncture with a 27-gauge spinal needle, bupivacaine 5 mg ml^{-1} in either 0.9% or 8% glucose was injected in a dose of 0.3 mg kg^{-1}. Maximum cephalad spread and regression of block were tested by transcutaneous electrical stimulation. Success rate, spread and duration of sensory block were similar in both groups. The highest median level of sensory block was T4 (10–90th percentiles T1–T7) in the 0.9% glucose group and T4 (T1–T5) in the 8% glucose group. Time to two segment regression of block was 83 (50–143) min in the 0.9% glucose and 85 (53–150) min in the 8% glucose group. The incidence of adverse effects was similar. Six children were given etilefrin to treat hypotension and six atropine for bradycardia. Nausea was associated with a high level of block. Shivering was detected in 16 children.

Br J Anaesth 2000; **84**: 59–62

Keywords: anaesthetic techniques, subarachnoid; anaesthetic local, bupivacaine; children; anaesthesia, paediatric; physics, baricity; complications, shivering; vomiting, nausea

Accepted for publication: June 23, 1999

Spinal anaesthesia is popular in both small children[1] and elderly people but less attention has been paid to school-age children. In Kuopio University Hospital, spinal anaesthesia has been used in 5000 paediatric patients over the past 10 yr. Spinal anaesthesia produces rapid onset, profound and uniformly distributed analgesia with good neuromuscular block. The amide local anaesthetics (bupivacaine and lidocaine) are used regularly, and spinal anaesthesia allows the use of a small dose with a low risk of systemic toxicity.

Baricity (weight of anaesthetic solution in relation to weight of cerebrospinal fluid (CSF)) is one of the most important factors claimed to influence distribution of local anaesthetic solutions in CSF.[2] Solutions administered most frequently are hyperbaric[3] as they produce more predictable block in both adults[4] and children.[5] Spinal anaesthetic solutions are rendered hyperbaric by adding glucose. However, commercially marketed solutions contain 8% glucose giving a density far in excess of that required to render them hyperbaric.

Studies in adults have found that addition of a small amount of glucose to increase the baricity of bupivacaine solution just into the hyperbaric range improved predictability of spinal block.[4 6] Different hyperbaric bupivacaine solutions have not been compared previously in children.

In this study, we have evaluated the role of baricity in block characteristics. Two different hyperbaric bupivacaine solutions (0.9% glucose and 8% glucose) were compared.

Patients and methods

The study was approved by our Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Both children and parents gave informed consent. We studied 107 children, ASA I–II, aged 7–18 yr, undergoing day-case surgery below the umbilicus. Patients with a known contraindication to spinal puncture, such as increased intracranial pressure, haemorrhagic diathesis or infection at the puncture site, were excluded. Children with a neurological disorder, or allergy to bupivacaine or other local anaesthetics were also excluded. Data were collected between December 1997 and February 1999 and some of the results of these patients have already been published[7]

We used a double-blind, randomized, parallel group, prospective study design. Patients were allocated randomly (computer-generated) to receive spinal anaesthesia with

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

either bupivacaine 5 mg ml^{-1} in 8% glucose (Marcain Spinal, Astra, Södertelje, Sweden) (bupivacaine–8% glucose group) or bupivacaine 5 mg ml^{-1} in 0.9% glucose (bupivacaine–0.9% glucose group). The dose of 0.3 mg kg^{-1} was based on our previous study of spinal anaesthesia in children.[5] Commercial ampoules of hyperbaric bupivacaine 5 mg ml^{-1} (in 8% glucose) and isobaric bupivacaine 5 mg ml^{-1} (in normal saline) with erased drug names were prepared and coded in the hospital pharmacy. Their identical appearance allowed blinding of the study. Local anaesthetic (4 ml) from a coded ampoule was mixed with 0.5 ml of hyperbaric bupivacaine. If the coded ampoule contained hyperbaric bupivacaine, mixing resulted in bupivacaine in 8% glucose; if the coded ampoule contained isobaric bupivacaine, this resulted in bupivacaine in 0.9% glucose. The baricity of bupivacaine in 8% glucose was 1.025 and that of bupivacaine in 0.9% glucose 1.005 at room temperature.

Children were not allowed solid food for 6 h but clear fluids were allowed up to 2 h before induction of anaesthesia. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally, up to a maximum dose of 10 mg. EMLA cream was used at the lumbar and venepuncture sites. An infusion of 0.9% saline was given at a rate of 5–10 ml kg^{-1} h^{-1}. Ketoprofen 2 mg kg^{-1} i.v. or rectal paracetamol 40 mg kg^{-1}, or both, were given for pre-emptive pain treatment.

Intraoperative monitoring consisted of non-invasive arterial pressure measurements every 5 min, continuous ECG, ventilatory frequency, peripheral arterial oxygen saturation and end-tidal carbon dioxide concentration using a nasal adapter. Appropriate treatment was given if systolic arterial pressure or heart rate decreased to less than 75% of baseline. All adverse effects were recorded.

Midazolam 0.03–0.05 mg kg^{-1} or thiopental 1–3 mg kg^{-1} i.v. were used for sedation in children who felt uncomfortable after premedication or during operation, or expressed a wish. Sedation was used in 53 children (thiopental in 30 and midazolam in 23 children) with similar distributions in both groups. All sedated children were administered oxygen and monitored closely by the anaesthetist or anaesthetic nurse.

Lumbar puncture was performed in the lateral decubitus position using a midline approach at the L3–4 or L4–5 interspace. Standard 27-gauge, 90-mm long spinal needles (Yale, Becton Dickinson, Meylan, Spain or Pencan, B Braun, Mellsungen, Germany) were used for spinal puncture. The bevel and orifice of the needle were facing laterally, parallel to the longitudinal dural fibres. Correct placement was verified by free aspiration of CSF. After injection of local anaesthetic, free aspiration of CSF was verified again and the child was placed in the supine, horizontal position. During spinal puncture the following variables were recorded: interspace used; number of skin punctures; need for redirection of needle; degree of difficulty of CSF aspiration (1=easy, 2=difficult, 3=impossible); and time to complete the block.

If there were signs of inadequate spread or duration of spinal anaesthesia in relation to the operation performed, fentanyl 1 μg kg^{-1} i.v. was given for supplementary analgesia. The cases were recorded.

An electric stimulator (Microstim Plus, Neuro Technology, Houston, TX, USA) was used to evaluate the width of the analgesic area, 15 and 30 min after injection of the anaesthetic. The metal electrodes of the device were moved in a rostral direction along the surface of the trunk using continuous high-frequency stimulation (50 Hz, pulse width 0.2 ms, amplitude 30–60 mA) until the child reported mild pain, indicating the upper border of the analgesic area. Amplitude was adjusted to the lowest level so that the response could just be elicited. The procedure was repeated until the level of the first painful segment was confirmed. Motor block was assessed using a modified Bromage scale recording the child's ability to flex the ankle, knee and hip (0=no motor block, 3=complete motor block of the legs and feet).

After operation, children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and regression of block. Regression of sensory block by two segments was tested every 5 min and the time recorded. If the child was in pain, fentanyl 1 μg kg^{-1} i.v. was given and the time recorded.

Patients were discharged when they were awake, able to walk unaided, had stable vital signs for at least 1 h, had no pain or only mild pain, had no nausea, retching or vomiting, and were able to tolerate clear fluids. Time to discharge was measured from spinal puncture to actual discharge from the hospital/PACU. After operation (at home) children were prescribed ibuprofen tablets 40 mg kg^{-1} day^{-1} in four divided doses. Parents were encouraged to give ibuprofen on the first night and first postoperative day, even if the child did not seem to be in pain. Later parents were told to give analgesics on an 'as required' basis. Follow-up of the children at home was recorded using a diary.

Power analysis suggested that 48 children were required in each group for a 90% chance at the 0.05 level of significance of detecting a 10% difference in success rate between groups. Categorical data were tested using the chi-square test. For continuous data the Mann–Whitney test was used. Association between independent variables was tested by linear regression analysis. Results are presented as median (10–90th percentiles), number (%) of cases or the square of the correlation coefficient (r^2) with 95% confidence intervals (CI), as appropriate. The level of statistical significance was set as $P<0.05$.

Results

Patient data (Table 1) and the characteristics of spinal puncture were comparable between groups (Table 2). Orthopaedic surgery was performed in 84 children; 23 underwent urological surgery, herniotomy, orchidopexy or circumcision.

Table 1 Patient characteristics (median (10–90th percentiles) or number of patients)

	Bupivacaine in 0.9% glucose ($n=55$)	Bupivacaine in 8% glucose ($n=52$)
Sex (M/F)	27/28	24/28
Weight (kg)	52 (27–65)	48 (30–64)
Height (cm)	156 (128–176)	157 (135–172)
Age (yr)	13 (8–16)	13 (8–16)
ASA I/II	44/11	38/14

Table 2 Characteristics of the spinal puncture in the two groups (median (10–90th percentiles) or number of patients)

	Bupivacaine in 0.9% glucose ($n=55$)	Bupivacaine in 8% glucose ($n=52$)
Interspace used for spinal puncture		
L3–4	20	17
L4–5	35	35
Repeated skin punctures	4	6
Redirection of needle	13	13
CSF aspiration easy/difficult	50/5	49/3
Appearance of CSF at the hub (s)	2 (1–4)	2 (1–4)
Time to complete (s)	40 (30–85)	40 (30–114)

Table 3 Success rate of spinal anaesthesia in the two groups (number (%)) *Fentanyl was administered for one child after an initially complete block after 55 min; **fentanyl was administered after an initially complete block after 115 min for one child, ***another was one of the failures

	Bupivacaine in 0.9% glucose ($n=55$)	Bupivacaine in 8% glucose ($n=52$)
Sensory block		
Complete	52 (95)	51 (98)
Fentanyl i.v.	3 (5)*	1 (2)**
Motor block		
Complete	53 (96)	52 (100)
Some movement	2 (4)***	

Table 4 Characteristics of sensory block in the two groups (median (10–90th percentiles)). Times are after spinal puncture

	Bupivacaine in 0.9% glucose ($n=55$)	Bupivacaine in 8% glucose ($n=52$)
Height of sensory block (dermatome)	T4 (T1–T7)	T4 (T1–T5)
Regression of block by two segments (min)	83 (50–143)	85 (53–150)
Regression of block to T7 (min)	90 (59–161)	103 (61–180)
Regression of block to T10 (min)	112 (63–178)	115 (66–180)
Time to first dose of rescue analgesic (min)	210 (88–337)	181 (120–279)
Time to discharge from hospital (min)	237 (147–352)	240 (180–330)

Table 5 Perioperative adverse effects of the spinal anaesthesia in the two groups (number (%)) *One patient vomited

	Bupivacaine in 0.9% glucose ($n=55$)	Bupivacaine in 8% glucose ($n=52$)
Hypotension	1 (2)	5 (10)
Bradycardia	3 (5)	3 (6)
Nausea	11 (20)*	10 (19)
Shivering	7 (13)	9 (17)

The success rate of spinal block was high in both groups with no differences between groups (Table 3). Four children required supplementation with fentanyl 1 µg kg^{-1}, three in the bupivacaine–0.9% glucose group and one in the bupivacaine–8% glucose group.

There was a similar variation in cephalad spread of sensory block in both groups (Table 4). Maximum extent of block was independent of age, weight, height or interspace used for spinal puncture.

Regression of block was similar in both groups. Regression of sensory block by two segments correlated with the age of the child in the bupivacaine–8% glucose group (r^2= 0.21, time=1.7+0.6×(age in months); CI for b=0.20–0.98), but not in the bupivacaine–0.9% glucose group.

Rescue analgesics were administered to 42 children in the PACU: 25 (49%) in the bupivacaine–8% glucose group and 17 (31%) in the bupivacaine–0.9% glucose group. Time to the first dose of analgesic was similar in both groups (Table 4).

There were no differences between groups in the incidence of adverse effects (Table 5). Six children were given etilefrin i.v. (Effortil, Boehringer Ingelheim, Ingelheim am Rhein, Germany) for hypotension. Six children were given atropine i.v. to treat bradycardia. Twenty-one (20%) children had nausea, but only one child vomited once. Nausea was mild (median 3 on a 10-cm VAS) and did not require treatment. Only two (7%) children suffered nausea when the height of the block was less than T4. Sixteen (15%) children experienced shivering in the PACU.

Children were discharged after a median time of 237 min in the bupivacaine–0.9% glucose group and after 240 min in the bupivacaine–8% glucose group (Table 4). In both groups there was a similar positive correlation between the age of the child and time to discharge from hospital: r^2= 0.22, time=97+1.0×(age in months), CI for b=0.47–1.5) in the bupivacaine–0.9% glucose group; and r^2= 0.18, time=97+0.97×(age in months), CI for b=0.36–1.6 in bupivacaine–8% glucose group.

Post-dural puncture headache occurred in three children in the bupivacaine–0.9% glucose group and in one child in the bupivacaine–8% glucose group. All four had mild symptoms which resolved in 1 or 2 days.

Discussion

We have compared the anaesthetic effects of bupivacaine 5 mg ml^{-1} in 0.9% and in 8% glucose solutions. Thus baricity was the main factor responsible for differences in spinal block. In agreement with the findings of Wildsmith and co-workers,[4 6] observed in adults, a slightly hyperbaric bupivacaine solution produced a predictable sensory block but the spread of the block did not show the narrow range observed in adults. In this study, the success rate of spinal anaesthesia with bupivacaine in 8% glucose was high as only one child required fentanyl and sedation to complete surgery. In our previous study with hyperbaric bupivacaine in children, a similar high success rate was verified compared with isobaric bupivacaine.[5]

We measured the analgesic area using transcutaneous electrical stimulation (TES). TES has been found to be equivalent to surgical incision;[8] it is a reproducible stimulus and is better than pinprick for assessment of height and duration of anaesthesia and analgesia in children.[5] However, it is important to adjust the amplitude to the lowest possible level to avoid unnecessary distress.

The results of our study confirm our earlier findings[5] that in school-age children, bupivacaine 0.3 mg kg^{-1} produced median sensory block to T4 with a median duration of 80–85 min. Duration of the block was adequate. However, the maximum extent of block was unnecessarily high as one-fifth of children had mild nausea during surgery. This warrants further study of a smaller dose of bupivacaine than 0.3 mg kg^{-1}.

Hypotension and bradycardia are normal physiological responses during spinal anaesthesia because of sympathetic fibre block.[9] In small children, cardiovascular stability during spinal anaesthesia is good[5 10] in contrast with school-age children (as observed in this study). Furthermore, in adults, spinal block with extensive spread impairs central thermoregulatory control.[11] Fifteen percent of children in our study experienced shivering during recovery of spinal block. Thus avoidance of extended block is also essential to counteract hypothermia.

In summary, we have demonstrated that the use of bupivacaine containing 0.9% glucose produced a similar spinal anaesthesia in school-age children as bupivacaine in 8% glucose. Spinal anaesthesia was associated with a high success rate and relatively low incidence of adverse effects.

References

1 Abajian JC, Mellish RW, Browne AF, Perkins FM, Lambert DH, Mazuzan JE. Spinal anesthesia for surgery in the high-risk infant. *Anesth Analg* 1984; **63**: 359–62

2 Bridenbaugh PO, Green NM. Spinal (subaracnoid) neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain.* Philadelphia: JB Lippincott, 1988; 213–51

3 Sethna NF, Berde CB. Paediatric regional anesthesia. In: Gregory GA, ed. *Paediatric Anesthesia.* New York: Churchill Livingstone, 1994, 281–317

4 Bannister J, McClure JH, Wildsmith JA. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine. *Br J Anaesth* 1990; **64**: 232–4

5 Kokki H, Tuovinen K, Hendolin H. Spinal anaesthesia for paediatric day-case surgery: a double-blind, randomized, parallel group, prospective comparison of isobaric and hyperbaric bupivacaine. *Br J Anaesth* 1998; **81**: 502–6

6 Sanderson P, Read J, Littlewood DG, McKeown D, Wildsmith JA. Interaction between baricity (glucose concentration) and other factors influencing intrathecal drug spread. *Br J Anaesth* 1994; **73**: 744–6

7 Kokki H, Heikkinen M, Turunen M, Vanamok, Hendolin H. Needle design does not affect the success rate of spinal anaesthesia or the incidence of postpuncture complications in children. *Acta Anaesth Scand* 1999, in press

8 Petersen-Felix S, Zbinden AM, Fischer M, Thomson DA. Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. *Anesthesiology* 1993; **79**: 959–65

9 Covino BG, Scott DB, Lambert DH. *Handbook of Spinal Anaesthesia and Analgesia.* Fribourg, Switzerland: Mediglobe SA, 1994

10 Saint-Maurice C. Spinal block. In: Saint-Maurice C, Steinberg OS, eds. *Regional Anaesthesia in Children.* Fribourg, Switzerland: Mediglobe SA, 1990; 119–25

11 Leslie K, Sessler DI. Reduction in the shivering threshold is proportional to spinal block height. *Anesthesiology* 1996; **84**: 1327–31

British Journal of Anaesthesia 84 (1). 63–6 (2000)

Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children

T. Katoh*, S. Kobayashi, A. Suzuki, S. Kato, T. Iwamoto, H. Bito and S. Sato

Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine,
3600 Handa-cho, Hamamatsu, 431-3192 Japan
**Corresponding author*

We studied 61 healthy ASA I patients (aged 2–6 yr) to determine if fentanyl affects the minimum alveolar concentration which blocks adrenergic responses to skin incision (MAC-BAR) in 50% of children in the presence of 60% nitrous oxide. Patients were allocated randomly to one of three fentanyl groups to receive 0, 2 or 4 μg kg^{-1}. Patients also received sevoflurane at a preselected end-tidal concentration according to an 'up-and-down' design. After a steady-state sevoflurane concentration had been maintained for at least 15 min, fentanyl was given i.v. Skin incision was performed 5 min after administration of fentanyl. The response was considered positive if heart rate (HR) or mean arterial pressure (MAP) increased by 15% or more. The MAC-BAR of sevoflurane was 1.45 MAC (95% confidence intervals 1.25–1.65 MAC), and this was reduced markedly to 0.63 MAC and 0.38 MAC by addition of fentanyl 2 and 4 μg kg^{-1}, respectively. A ceiling effect was not observed and there was a significant difference between the 2 and 4 μg kg^{-1}groups.

Br J Anaesth 2000; **84**: 63–6

Keywords: anaesthesia, paediatric; anaesthetics volatile, sevoflurane; analgesics opioid, fentanyl, potency, anaesthetic, MAC; interactions (drug); children

Accepted for publication August 3, 1999

In paediatric anaesthesia, sevoflurane is suitable because it has a pleasant smell, does not irritate the airways, and its blood-gas partition coefficient is similar to that of desflurane or nitrous oxide. The minimum alveolar concentration (MAC) of sevoflurane, isoflurane and desflurane (i.e. prevents movement in response to skin incision in 50% of a population) is less than that which blocks adrenergic responses to skin incision (MAC-BAR).[1 2] The effect of fentanyl in reducing sevoflurane requirements for blunting cardiovascular responses after surgical incision has been demonstrated recently in adults.[2] The ability of opioids to decrease anaesthetic requirements in children has not been studied for any potent inhalation anaesthetic. In this study, we investigated the effect of fentanyl on sevoflurane requirements for blunting cardiovascular responses to surgical incision in children.

Patients and methods

After obtaining approval from the Departmental Ethics Committee and informed consent from the parent or guardian of each patient, we studied 61 children, ASA I, aged 2–6 yr, scheduled for surgery under general anaesthesia. Exclusion criteria were history of cardiac and pulmonary abnormalities, neurological disorders, hypertension and use of medications which may affect arterial pressure, heart rate or MAC values of inhaled anaesthetics Preanaesthetic laboratory values were normal.

Patients fasted for at least 4 h before surgery and received no premedication. Standard monitoring included electrocardiogram, pulse oximetry and non-invasive arterial pressure. General anaesthesia was induced with sevoflurane and nitrous oxide in oxygen with a total fresh gas flow rate of 6 litre min^{-1}. An i.v. catheter was inserted for infusion of Ringer's lactate solution at a rate of 10 ml kg^{-1} h^{-1} The trachea was intubated without neuromuscular block. A steady-state end-tidal sevoflurane concentration was established and maintained for at least 15 min before skin incision.

Patients were allocated randomly to one of three fentanyl groups: group 1 received no fentanyl, and groups 2 and 3 received fentanyl 2 and 4 μg kg^{-1} i.v., respectively, over 30 s, 5 min before skin incision.

Gas was drawn continuously through a 19-gauge catheter, the tip of which was placed within 3 cm of the tracheal end of the tracheal tube, at a rate of 200 ml min^{-1}. Concentrations of sevoflurane, nitrous oxide, carbon dioxide and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland), which was calibrated before anaesthesia for each patient using a standard gas mixture. Lung ventilation was

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

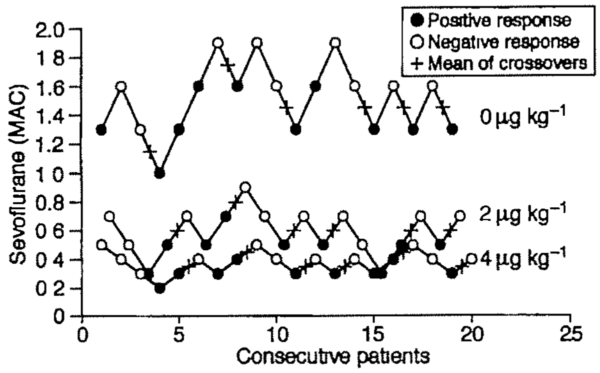


Fig 1 Consecutive target sevoflurane concentrations in each group. When a patient showed a positive cardiovascular response (an increase in heart rate or mean arterial pressure of more than 15%) at skin incision, the anaesthetic concentration for the next patient in each group was decreased by 0.3, 0.2 or 0.1% for group 1, 2 or 3, respectively. Conversely, when a patient showed a negative cardiovascular response, the anaesthetic concentration for the next patient was increased by the same amount

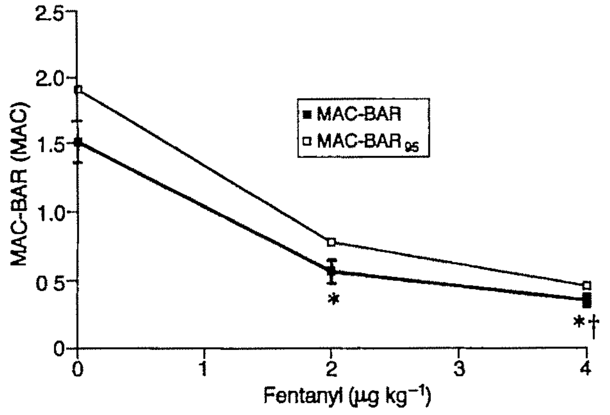


Fig 2 The sevoflurane concentration required to prevent cardiovascular responses to skin incision in 50% or 95% of patients (MAC-BAR or MAC-BAR$_{95}$, respectively), with and without fentanyl. Each dose of fentanyl significantly reduced the MAC-BAR of sevoflurane (*P<0.05), and there was a significant difference between the effects of the two fentanyl doses (†P<0.05). Data are mean (95% confidence intervals).

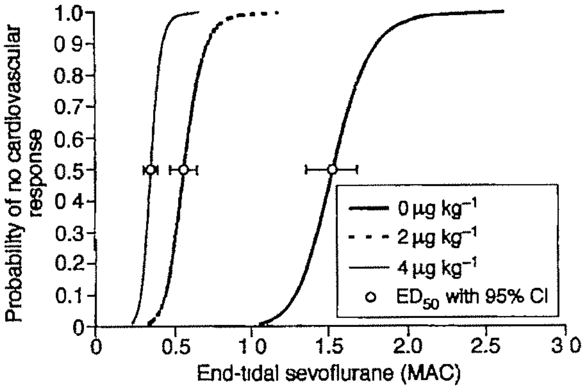


Fig 3 Probability of no cardiovascular response at skin incision during sevoflurane anaesthesia in combination with fentanyl 0, 2 or 4 μg kg^{-1}, administered 5 min before skin incision. Error bars represent 95% confidence limits around MAC-BAR.

controlled manually in each patient to achieve adequate end-tidal volumes for sampling. End-tidal carbon dioxide partial pressures were maintained at 3.9–4.6 kPa during the study. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration at a constant value according to a preselected concentration. All patients also received 60% end-tidal nitrous oxide in oxygen. The target end-tidal concentrations of sevoflurane were maintained for at least 15 min before surgical incision.

Heart rate (HR) and mean arterial pressure (MAP) were measured and recorded at the following four times: on the ward with parents before the patient was brought to the operating room; 1 min before administration of fentanyl; 1 min before skin incision; and at 30-s to 1-min intervals for 5 min after skin incision. In the last period, the maximum consecutive MAP and HR measurements were selected as representative values. If MAP before incision decreased to less than 40 mm Hg, the patient was excluded from the study and treatment to restore arterial pressure was started immediately.

The 'up and down' method was used to determine MAC-BAR. The response of the preceding patient determined the concentration of the inhalation agent given to succeeding patients in each group. The initial concentrations of sevoflurane were 1.3, 0.9 and 0.5 MAC for groups 1, 2 and 3, respectively. The MAC value of sevoflurane was adjusted to the patient's age based on published data.[3–6] If the response of the preceding patient in that group was positive (an increase in either HR or MAP $\geq$15% above the value 1 min before incision), the end-tidal concentration given to the next patient was increased by 0.3, 0.2 or 0.1 MAC for group 1, 2 or 3, respectively. If the response was negative (neither HR nor MAP increased by <15%), the end-tidal concentration given to the next patient was decreased by the same amount. This rule tends to concentrate testing in the range of sevoflurane concentrations which gives a 50% probability of blocking cardiovascular responses.

Statistical analysis

Mean HR and MAP were calculated in each group based on the responses to skin incision after the first crossover. MAC-BAR values were calculated as the mean of six independent crossovers of response in which positive and negative responses were paired up for each group (Fig. 1). Data were also analysed using a logistic model to calculate the effective sevoflurane concentration required for blocking cardiovascular responses to skin incision in 50% and 95% (ED$_{50}$ and ED$_{95}$, respectively) of patients.[7] ED$_{95}$ was calculated directly from the best-fitting logistic curve. Data for MAC-BAR are expressed without the contribution of nitrous oxide.

Group data were analysed by analysis of variance or a Student's t test, with correction for multiple comparisons when appropriate (StatView 4.02; Abacus Concepts, Berkeley, CA, USA). Probability values <0.05 were considered statistically significant.

Table 1 Age, body weight, preanaesthetic and preincisional heart rate (HR), mean arterial pressure (MAP) and time between induction and incision (mean (SD or range)). HR and MAP values are averaged after crossover point. No differences between groups before anaesthesia. Significant difference of ($P<0.05$) from *no fentanyl group, †preanaesthetic value, ‡before fentanyl administration. [1]Values were at 5 min before incision, (fentanyl was not administered in this group)

Fentanyl dose (μg kg^{-1})	*n*	Age (yr)	Weight (kg)	*n* after first crossover point	On ward		Before fentanyl administration		Before incision		Time from induction of anaesthesia to incision (min)
					HR (beat min^{-1})	MAP (mm Hg)	HR (beat min^{-1})	MAP (mm Hg)	HR (beat min^{-1})	MAP (mm Hg)	
0	19	4.6 (2–6)	16.4 (3.4)	17	92 (12)	77 (8)	92 (12)[1]	57 (8)†[1]	90 (9)	57 (6)	28 (7)
2	19	4.4 (2–6)	16.9 (3.0)	16	88 (10)	81 (7)	90 (11)	65 (7)*†	81 (10)*†‡	62 (9)†‡	31 (9)
4	20	4.2 (2–6)	17.1 (3.6)	16	90 (12)	76 (6)	94 (12)	68 (6)*†	78 (11)*†‡	64 (7)*†‡	28 (9)

Results

Fifty-eight patients completed the investigation. Three patients in group 1 (no fentanyl) were excluded because MAP before incision decreased to less than 40 mm Hg. The groups did not differ significantly in age, body weight, HR or MAP on the ward or during the time between induction of anaesthesia and incision. During sevoflurane anaesthesia, MAP but not HR decreased in a concentration-dependent manner before administration of fentanyl. MAP and HR did not decrease from before administration of fentanyl to pre-incision values in patients who did not receive fentanyl during the 5-min waiting period. Fentanyl administration significantly decreased HR and MAP (Table 1). Individual responses are shown in Figure 1.

The MAC-BAR of sevoflurane was 1.45 MAC (95% confidence intervals (CI) 1.25–1.65 MAC) in the absence of fentanyl. Fentanyl 2 μg kg^{-1} significantly reduced the MAC-BAR to 0.63 MAC (95% CI 0.55–0.72 MAC). Fentanyl 4 μg kg^{-1} produced a further significant reduction in MAC-BAR to 0.38 MAC (95% CI 0.33–0.44 MAC) (Fig. 2).

ED_{50} and ED_{95} values for sevoflurane obtained from logistic analyses were 1.52 MAC (95% CI 1.36–1.67 MAC) and 1.92 MAC without fentanyl, 0.57 MAC (95% CI 0.48–0.65 MAC) and 0.78 MAC with fentanyl 2 μg kg^{-1} and 0.35 MAC (95% CI 0.31–0.40 MAC) and 0.46 MAC with 4 μg kg^{-1} (Fig. 3).

Discussion

In children, the anaesthetic requirements for sevoflurane in the presence of 60% nitrous oxide to block cardiovascular responses to skin incision were considerably higher than those required to block motor responses.[3 5] Ishizawa and Dohi reported that the MAC-BAR of halothane in children is 1.12 MAC in the presence of the same concentration of nitrous oxide used in our study.[8] However, there are important differences between the two studies with respect to the conditions and criteria used for the determination of MAC-BAR. Ishizawa and Dohi considered a 'positive' response as an increase in MAP or HR of 10% or more from preincision values, while we used 15% or more. This suggests that if we used the same criterion, a greater MAC-BAR value would have been obtained. Yamada and colleagues demonstrated that the suppressive action of sevoflurane on the cardiovascular response to noxious stimuli is weaker than that of halothane.[9]

Our data are new but not surprising. Daniel and colleagues demonstrated that isoflurane and 60% nitrous oxide blunted the cardiovascular response to skin incision at 1.3 MAC, and that fentanyl 1.5 and 3 μg kg^{-1} decreased the MAC-BAR of isoflurane by 58% and 69% using a similar method to ours.[1] The magnitudes of reduction in MAC-BAR obtained in our study (56% and 76% with fentanyl 1.5 and 3 μg kg^{-1}, respectively) were similar, despite the differences in doses of fentanyl. However, Daniel and colleagues found a ceiling effect for the reduction of the isoflurane MAC-BAR, while we found a significant difference in the MAC-BAR reduction with fentanyl 2 and 4 μg kg^{-1}. This suggests that a ceiling effect may not occur with these small doses of fentanyl in children.

In our study, we did not determine MAC-BAR in the absence of nitrous oxide because it would be at a clinically unacceptable high concentration and preincision arterial pressure would be depressed to levels that may be clinically unacceptable.

In adults, at a normal analgesic concentration not associated with respiratory depression, and 66% nitrous oxide, the MAC-BAR concentration of sevoflurane is almost equal to the end-tidal concentration at which 50% of patients respond to a verbal command (MACawake). Thus anaesthesia that inhibits haemodynamic responses is achieved with concentrations of sevoflurane and fentanyl that are associated with rapid awakening and yet adequate analgesia on removal of nitrous oxide.[2] In children, however, the effect of fentanyl on the MACawake has not been determined and therefore further study of the interaction of sevoflurane and fentanyl on MACawake is required.

References

1 Daniel M, Weiskopf RB, Noorani M, Eger EI II Fentanyl augments the blockade of the sympathetic response to incision (MAC-BAR) produced by desflurane and isoflurane *Anesthesiology* 1998, **88**: 43–9

2 Katoh T, Kobayashi S, Suzuki A, Iwamoto A, Bito H, Ikeda K. The effect of fentanyl on sevoflurane requirements for somatic and sympathetic responses to surgical incision. *Anesthesiology* 1999; **90**: 398–405

3 Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–24

4 Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1987; **66**: 301–3

5 Katoh T, Ikeda K. Minimum alveolar concentration of sevoflurane in children. *Br J Anaesth* 1992; **68**: 139–41

6 Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Can J Anaesth* 1988; **35**: 153–6

7 Waud DR. On biological assays involving quantal responses. *J Pharmacol Exp Ther* 1972; **183**: 577–607

8 Ishizawa Y, Dohi S. Halothane concentrations required to block the cardiovascular responses to incision (MAC CVR) in infants and children. *Can J Anaesth* 1993; **40**: 18–23

9 Yamada K, Shingu K, Kimura H, *et al.* Circulatory and catecholamine responses to tracheal intubation and skin incision during sevoflurane, isoflurane, or halothane anesthesia. *J Anesth* 1997; **11**: 111–16

British Journal of Anaesthesia 84 (1) 67–73 (2000)

BJA

LABORATORY INVESTIGATION

Microdialysis study of the blood–brain equilibration of thiopental enantiomers

L. E. Mather[1]*, S. R. Edwards[1], C. C. Duke[2] and M. J. Cousins[1]

[1]*Department of Anaesthesia and Pain Management, University of Sydney at Royal North Shore Hospital,*
St Leonards, NSW 2065, Australia. [2]*Department of Pharmacy, University of Sydney,*
Sydney, NSW 2006, Australia

**Corresponding author*

Thiopental is a racemate of equimolar R- and S-thiopental enantiomers that have different potencies in laboratory experiments. We measured concentrations of R- and S-thiopental in plasma, tissues and brain microdialysate of rats after computer-controlled infusion of thiopental i.v. to a plasma concentration of 40 μg ml^{-1} for 20 min in two pharmacokinetic studies. In study 1, animals were found to maintain their target plasma concentrations, which then decayed biphasically after infusion. Brain microdialysate concentrations of both enantiomers increased from about 3% of corresponding plasma concentrations at 1 min to 9% at 20 min. In study 2, thiopental concentrations were found to be highest at 20 min in CNS tissue, at 30 min in muscle and at 60 min in fat. Tissue:plasma distribution coefficients of R-thiopental were greater than those of S-thiopental when calculated from total or unbound plasma concentrations. We found no pharmacokinetic evidence to support differences between the thiopental enantiomers in rates of equilibration across the blood–brain barrier after infusion of rac-thiopental.

Br J Anaesth 2000; **84**: 67–73

Keywords: anaesthetics i.v., thiopental; brain, blood–brain barrier; pharmacokinetics, stereoisomers; measurement techniques, microdialysis; rat

Accepted for publication: July 2, 1999

The action of thiopental on the central nervous system (CNS) is exemplified by initial activation and subsequent depression of the electroencephalogram (EEG).[1 2] Thiopental, in common with many barbiturates, is a racemate. (The nomenclature used in this article is thiopental for the clinically used racemate (i.e. *rac*-, (RS)- or (±)-thiopental) or for the sum of enantiomers as would be measured for example in plasma and tissues by conventional achiral analyses; R- and S-thiopental are used for individual (R)-(+)- and (S)-(–)-thiopental enantiomers. As the signs of the optical rotations are not of significance to this article, they have been deleted for simplicity. By definition, a racemate contains equal quantities of both enantiomers.) Although currently there are no data for thiopental, various studies have found differences in CNS effects between barbiturate enantiomers. For example, R-pentobarbital is predominantly excitatory and S-pentobarbital predominantly inhibitory in cultured mouse spinal neurones;[3] the (+)-enantiomer of the related barbiturate, 5-(1,3-dimethylbutyl)-5-ethyl barbituric acid (DMBB), causes seizures whereas the (–)-enantiomer induces only a pre-anaesthesia excitation.[4]

In an attempt to determine if the biphasic CNS effects of thiopental, as shown on the EEG, could be related to a preferential rate of uptake of a predominantly excitatory thiopental enantiomer, we examined the rates of influx and efflux of thiopental enantiomers from sheep brain after i.v. infusion of thiopental. There were no significant differences between the enantiomers in rates of influx and efflux.[5] As this analysis was based on measurement of flux averaged across the whole brain, it may not have been indicative of the microenvironment generating the predominant EEG response, as measured in other studies. Hence we performed a more sensitive analysis, based on the rate of equilibration of thiopental enantiomers between plasma and extracellular fluid (ECF), of selected brain areas using microdialysis in rats. This technique is considered to be particularly well suited to investigations of drug uptake into the CNS[6–9]

Materials and methods

The studies were approved by the Institutional Animal Care and Ethics Committee. Two study designs were used, both

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

with jugular vein infusions of thiopental in rats to achieve and maintain a constant target plasma concentration of 40 μg ml^{-1} for 20 min, followed by a washout period of 40 min (total dose 54.5 mg kg^{-1}). The infusion rates were determined and controlled by Stanpump software operating with previously described pharmacokinetic data for thiopental and implemented on a personal computer.[10] In study 1, microdialysis of the striatum (n=6) or hippocampus (n=7) was used to determine the rate of equilibration of the thiopental enantiomers across the blood–brain barrier. In study 2, total and unbound plasma thiopental enantiomer concentrations, together with CNS, muscle and fat concentrations, were measured after infusion at 20, 30 and 60 min (n=6 at each time).

Young adult male Wistar rats (350–400 g), housed individually after surgery, were maintained in a constant 12-h light–dark cycle at 23°C and allowed free access to food and water. Experimental procedures were performed within 3–5 days of surgery when body weight had returned to within 5% of baseline.

Anaesthesia was induced with an initial dose of pentobarbital 30 mg kg^{-1} i.p. followed 5 min later by ketamine 45 mg kg^{-1} i.p.; both drugs were delivered in 1 ml of 0.9% saline. Chronic indwelling cannulae (silastic laboratory tubing, 0.025″ id×0.047″ od and 0.020″ id×0.037″ od, respectively) were implanted into the jugular vein and carotid artery to allow simultaneous venous infusion and arterial blood sampling. The cannulae were tunnelled under the skin, externalized above the neck anterior to the scapulae and filled with a solution of polyvinylpyrrolidone 6 g in sodium heparin 5 ml (1000 u. ml^{-1}) to prevent occlusion. On completion of surgery, animals were administered amoxycillin 85 mg kg^{-1} i.m., buprenorphine 0.15 mg kg^{-1} s.c. and 0.9% saline 10 ml s.c. for fluid replacement. Amoxycillin 85 mg kg^{-1} i.m. was administered the following morning. Postoperative body weight and fluid intake were monitored.

For the infusions, sodium thiopental (Pentothal, Abbott Australasia Pty Ltd) was dissolved in deionized water to give a final concentration of 10 mg ml^{-1} (9.2 mg ml^{-1} as free acid) and contained heparin 2 u. ml^{-1}.

Study 1: microdialysis

Anaesthesia was induced with 5% halothane in oxygen 1 litre min^{-1}; rats were mounted in a stereotaxic frame (Kopf model 900) and an anaesthetic mask was fitted around the rat's head and the nose bar of the stereotaxic frame. The concentration of halothane was reduced to 2% at 0.5 litre min^{-1} until implantation of the microdialysis probe was completed. A midline incision was made to expose the skull, and coordinates for the corpus striatum (A/P +0.4 mm, L 3.0 mm, D/V –6.6 mm) and hippocampus (A/P –5.2 mm, L 5.0 mm, D/V –6.0 mm) were measured from the bregma.[11] A circular region of the skull was removed with a dental drill to expose the brain surface and the dura was removed gently. The dorsal–ventral coordinate was obtained from the surface of the brain. The probe was lowered gradually into position, halothane was reduced to 1.0% and the probe environment was allowed to stabilize for 30 min.[6 12 13] Oxygen flow was maintained at 0.5 litre min^{-1} for the duration of the study and body temperature was maintained at 37–38°C with a heating pad.

Microdialysis probes of concentric design (CMA12/3 mm membrane; CMA Microdialysis AB, Solna, Sweden) were perfused at 5 μl min^{-1} with Ringer's solution (NaCl 140 mmol litre^{-1}, KCl 4 mmol litre^{-1} and $CaCl_2$ 2.5 mmol litre^{-1}) using a microsyringe (CMA 2.5 ml) and microinjection pump (CMA/100), while microdialysate samples were collected using a CMA/200 microsampler. The performance of the probes was assessed before commencing the study by examining volume delivery and recovery (ratio of thiopental concentration in microdialysate:concentration surrounding the probe) *in vitro* for a solution of thiopental (100 μg ml^{-1} in Ringer's solution). Probes performing satisfactorily were reused, and >2 h washout time was allowed before the study commenced.

Microdialysate sampling began immediately after infusion of thiopental into the jugular vein had commenced. Arterial blood samples (0.1 ml) were collected at 0, 1, 2, 5, 10, 20, 21, 22, 25, 30, 40 and 60 min; the samples were replaced with 0.9% saline 0.2 ml followed by 0.1 ml of heparin 10 u. ml^{-1} in 0.9% saline. After centrifugation, plasma aliquots (50 μl) were stored frozen (–20°C for up to 4 weeks) until analysis. Microdialysate samples were collected over 5-min intervals for 60 min into 250-μl polypropylene vials containing 50 μl of internal standard (5-ethyl-5-hexyl barbituric acid 2 μg ml^{-1} in Ringer's solution) and assayed immediately after the study. At the end of each study, the animal was killed by barbiturate overdose and the brain removed, fixed in formalin (10% v/v in 0.9% saline) and sliced with a scalpel blade, through the coronal plane, to expose the cannula tract. Correct placement of the cannula in the striatum or hippocampus was verified visually by reference to the anatomical atlas of Paxinos and Watson.[11]

Microdialysis recovery of thiopental *in vivo* was estimated by a single point calibration procedure, adapted from the zero net flux technique,[9] whereby loss of solute across the probe (equation (1)) is assumed to be equivalent to recovery of solute measured from a solution surrounding the probe.[12] At the end of sampling, thiopental 100 μg ml^{-1} in Ringer's solution was perfused through the probe at 5 μl min^{-1} and after equilibration for 20 min, microdialysate was collected for 10 min. However, a directional-dependent diffusion effect may result from membrane–solute interactions.[14] Thus the ratio of thiopental *recovery* to *loss* was determined for a 100-μg ml^{-1} solution of thiopental in Ringer's solution, either surrounding the probe or in the perfusate, and was found to be 0.64. Hence microdialysate concentrations were related to apparent extracellular fluid (aECF) concentrations using equations (2) and (3). The lag time required for perfusate to traverse the dead volume of the dialysate tubing and probe was determined separately.

Loss=(perfusate concentration–dialysate concentration)/perfusate concentration (1)

aECF concentration=microdialysate concentration/recovery (2)

aECF concentration=microdialysate concentration/(loss×0.64) (3)

Study 2: tissue and free plasma concentrations of thiopental enantiomers

Three groups of six rats were anaesthetized by infusion of thiopental into the jugular vein as in study 1. Blood and tissue samples were obtained from anaesthetized animals at 20, 30 and 60 min after the start of infusion. After thoracotomy, blood was withdrawn by cardiac puncture using a heparinized 21-gauge needle and syringe, and plasma was separated by centrifugation. CNS tissue samples were obtained from the cortex, striatum, hippocampus, cerebellum, brachial and sacral spinal intumescences; epididymal fat and adductor muscle were also sampled. Samples were stored at –80°C until analysed.

Binding of thiopental enantiomers was determined by equilibrium dialysis of the harvested plasma (adjusted to pH 7.4 with NaH_2PO_4 0.5 mol $litre^{-1}$ immediately before dialysis) against phosphate buffer (0.067 mol $litre^{-1}$, pH 7.4) in cells (Plexiglas 2.5 cm diameter, 0.5 cm depth) separated by pre-washed cellulose membranes. The cells were incubated at 37°C for 8 h with gentle shaking.[15]

Thiopental enantiomer assays

R- and S-thiopental concentrations were determined using our previously reported HPLC procedure with micro-modifications.[16] Plasma aliquots (50 μl in 1.5-ml Eppendorf tubes) were extracted with ethyl acetate in hexane (1.1 ml, 5% v/v) after addition of internal standard (5-ethyl-5-hexyl barbituric acid 50 μg ml^{-1}, 50 μl) and H_3PO_4 (10 μl, 2 mol $litre^{-1}$). Samples were shaken vigorously (1 min), centrifuged (7000 rpm, 2 min) and frozen on dry ice (15 min) before the organic layer was decanted and evaporated to dryness in a rotary vacuum bench evaporator (40°C). The residue was reconstituted in Na_2HPO_4 solution (200 μl, 10 mmol $litre^{-1}$ containing 30% v/v isopropanol); an aliquot (10 μl) was injected onto the column. Tissue samples were homogenized (50–100 mg ml^{-1}) in Na_2HPO_4 (0.2 mol $litre^{-1}$). An aliquot (200 μl) was taken, internal standard (100 μl) was added and the sample was extracted with hexane (1.0 ml) by shaking vigorously (1 min). After centrifugation (2 min, 7000 rpm), the organic layer was decanted and discarded, the sample was resuspended by sonication, vortex-mixed, acidified with H_3PO_4 (20 μl, 2 mol $litre^{-1}$) and extracted with ethyl acetate in hexane (5% v/v) as before. Microdialysate samples were injected (60 μl) without prior extraction. The mobile phase was delivered at a flow rate of 0.9 ml min^{-1} and consisted of phosphate buffer (100 mmol $litre^{-1}$, pH 6.3) containing isopropanol (4.5% v/v).

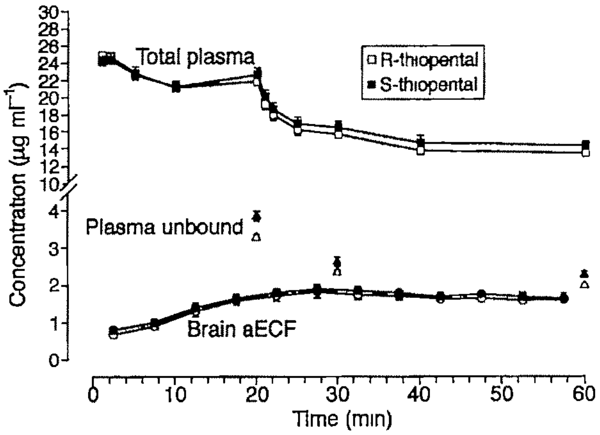


Fig 1 Mean (SEM) total and unbound plasma and brain aECF concentrations of R- and S-thiopental in rats (n=6) undergoing striatal microdialysis during infusion of thiopental to a combined enantiomer target of 40 μg ml^{-1} for 20 min.

Data analysis

Data from one animal undergoing striatal microdialysis in study 1 were rejected because of leakage of thiopental from the syringe connection. Pairwise comparisons of relevant R- and S-thiopental concentrations were performed using the Student's t test for paired data; enantiomeric bias was deemed to have occurred if the ratio of concentrations or the areas under the relevant concentration time curves (AUC) for (S:R) thiopental enantiomers differed from unity (Student's one sample t test). Respective plasma and aECF data in the striatal and hippocampal microdialysis studies were compared using the Student's t test. Relevant respective CNS tissue thiopental enantiomer concentrations and their (S:R) enantiomer ratios, and tissue:plasma distribution coefficients for the thiopental enantiomers and their (S:R) ratios were compared across regions and times by two-factor analysis of variance (ANOVA). Peripheral tissue samples were compared by one-factor ANOVA. Significance (ANOVA) was followed by pairwise comparisons performed by the method of least significant differences. Distribution coefficients for peripheral tissues and plasma binding were compared using the Student's t test.

Results

Study 1: microdialysis

Total thiopental enantiomer plasma concentrations remained near the target concentration of 40 μg ml^{-1} during the infusion period (Figs 1, 2). There was no overall difference in plasma thiopental concentrations or AUC values between the groups of animals who underwent striatal or hippocampal microdialysis; however, plasma thiopental concentrations were lower in the hippocampal group for the 2-min samples ($P<0.05$).

The thiopental enantiomer plasma concentration (S:R) ratio increased over time and was significantly higher at 60 min than at 1 min in both groups (striatal $P<0.05$;

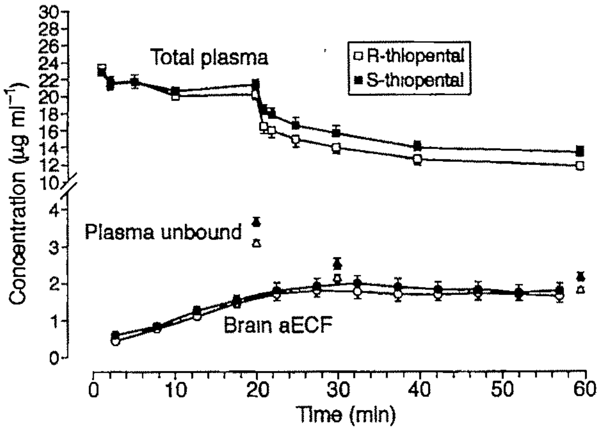


Fig 2 Mean (SEM) total and unbound plasma and brain aECF concentrations of R- and S-thiopental in rats (n=7) undergoing hippocampal microdialysis during infusion of thiopental to a combined enantiomer target of 40 µg ml^{-1} for 20 min

hippocampal $P<0.0005$). aECF concentrations of both thiopental enantiomers increased until after the end of infusion (i.e. time-related slopes >0; striatal $P<0.002$; hippocampal $P<0.0002$); aECF thiopental concentrations in the 2.5-min fraction were lower in the hippocampal than in the striatal group ($P<0.05$). There was no significant difference between groups in AUC values for aECF thiopental concentrations when compared over the duration of the infusion. However, the aECF:plasma ratio for the 2.5-min fraction was significantly lower for the hippocampal group ($P<0.05$). Mean aECF thiopental concentrations in both groups peaked in the 27.5-min fraction. Taking into account a system dead volume lag time of 2.5 min and a further diffusional delay of 2.5 min in attaining maximal concentrations found in *in vitro* experiments, the effective peak aECF concentration of both enantiomers at both sites of microdialysis occurred at 22.5 min.

By 60 min, mean plasma thiopental concentrations in the striatal and hippocampal groups had decreased significantly to 63% ($P<0.0001$) and 59% ($P<0.0001$) of their respective end-infusion concentrations whereas the respective mean aECF concentrations had deceased to only 89% (ns) and 90% ($P<0.005$) of their respective peak concentrations. Mean aECF concentrations of S-thiopental usually exceeded those of R-thiopental. Whereas mean striatal aECF AUC values did not differ significantly, hippocampal AUC values of S-thiopental significantly exceeded those of R-thiopental ($P<0.05$) and enantiomeric bias ($P<0.01$) was also apparent.

Study 2: tissue and free plasma concentrations of thiopental enantiomers

Pairwise comparison of tissue concentration data (Table 1) indicated a bias towards higher concentrations of S-thiopental ($P<0.002$). Concentrations of both enantiomers were higher in spinal than in brain regions ($P<0.005$) but did not differ within the respective CNS regions. Concentrations of both enantiomers in all CNS regions decreased from 20 min (end of infusion). Muscle concentrations of S-thiopental were greater than those of R-thiopental at 20 min ($P<0.01$) (Table 1), and the (S:R) enantiomer concentration ratio did not differ between the three sampled times. Fat concentrations of S-thiopental were greater than those of R-thiopental at 20 ($P<0.025$), 30 ($P<0.01$) and 60 ($P<0.02$) min, and the (S:R) enantiomer concentration ratio did not differ with time. Fat concentrations of both enantiomers were significantly higher ($P<0.001$) at 60 min than at 20 min.

Table 1 Mean (SEM) concentrations of thiopental enantiomers and their relevant enantiomer ratios in the CNS and peripheral tissues in three groups (n=6) of rats after infusion with thiopental to a target plasma concentration of 40 µg ml^{-1} for 20 min. R *vs* S and S/R *vs* 1: $^{a}P<0.05$, $^{b}P<0.01$, $^{c}P<0.005$

Tissue	Time (min)	R-thiopental (µg g^{-1})	S-thiopental (µg g^{-1})	S/R ratio
Cortex	20	27.4 (1.1)	28.0 (1.3)	1.02 (0.01)
	30	21.3 (1.2)	21.7 (1.1)	1.02 (0.01)
	60	16.8 (1.3)	17.1 (1.4)	1.01 (0.03)
Striatum	20	29.1 (1.5)	28.4 (1.5)	0.98 (0.01)
	30	22.3 (0.9)	23.0 (1.0)	1.03 (0.01)
	60	16.9 (1.0)	17.0 (1.0)	1.00 (0.02)
Hippocampus	20	30.3 (1.3)	30.8 (1.0)	1.02 (0.01)
	30	20.3 (1.1)	21.2 (1.0)	1.05 (0.02)
	60	15.7 (0.8)	16.7 (1.1)	1.06 (0.02)
Cerebellum	20	30.5 (1.6)	30.9 (1.6)	1.01 (0.01)
	30	22.6 (0.5)	22.8 (0.7)	1.01 (0.01)
	60	17.1 (1.2)	17.5 (1.4)	1.02 (0.02)
Brachial cord	20	39.6 (3.3)	39.7 (3.0)	1.01 (0.01)
	30	28.4 (1.4)	29.2 (1.7)	1.02 (0.02)
	60	19.7 (2.0)	19.5 (2.2)	0.98 (0.02)
Sacral cord	20	37.1 (0.8)	37.2 (0.5)	1.00 (0.02)
	30	28.6 (0.6)	28.3 (0.6)	0.99 (0.02)
	60	21.0 (2.1)	21.0 (1.6)	1.01 (0.03)
Muscle	20^{b}	12.3 (1.1)	12.8 (1.1)	1.04 (0.01)^{b}
	30	14.3 (1.1)	14.8 (1.1)	1.04 (0.02)
	60	10.1 (1.2)	10.5 (1.3)	1.04 (0.02)
Fat	20^{a}	57.0 (7.1)	59.6 (7.1)	1.05 (0.02)^{a}
	30^{b}	74.0 (9.9)	77.3 (10.4)	1.04 (0.01)^{b}
	60^{a}	120.4 (9.9)	125.3 (10.7)	1.04 (0.01)^{c}

Plasma concentrations of both thiopental enantiomers at 20 min in study 2 (Table 2) were markedly higher than those at the same time from the same infusion regimen in study 1 (Figs 1, 2). This was attributed to blood concentration enrichment occurring while thiopental was being infused and blood was concurrently sampled by cardiac puncture. Subsequent statistical comparisons of tissue:plasma distribution coefficients (Tables 3, 4) were performed only on 30- and 60-min data; nevertheless, the 20-min data were suitable for the purpose of comparison of relative enantiomer concentrations. Total plasma concentrations of S-thiopental were greater than those of R-thiopental in each sample ($P<0.005$), with higher unbound fractions in the 30- ($P<0.005$) and 60- ($P<0.005$) min samples (Table 2).

Pairwise comparisons (Tables 3, 4) of tissue:plasma distribution coefficients across CNS regions showed that R-thiopental was greater than S-thiopental ($P<0.0001$) for the 30- and 60-min samples; the differences were larger

Table 2 Mean (SEM) plasma concentrations (unbound percentages) of thiopental enantiomers and their relevant enantiomer ratios in three groups ($n=6$ but $n=5$ for 20- and 30-min unbound fraction data) of rats after infusion of thiopental to a target plasma concentration of 40 µg ml^{-1} for 20 min. R *vs* S and S/R *vs* 1· [a]*P*<0 01; [b]*P*<0 02, [c]*P*<0.005; [d]*P*<0.001

Time (min)	Thiopental enantiomer	Plasma concentration (µg ml^{-1})	S/R ratio	Unbound fraction (%)	S/R ratio
20	R-thiopental	35.5 (3 8)[d]		18 8 (1 5)	
	S-thiopental	40.7 (3 6)		19 4 (1 7)	
			1 17 (0 05)[b]		1 03 (0 02)
30	R-thiopental	20 0 (0.8)[d]		14.5 (0 8)[d]	
	S-thiopental	23.0 (1 1)		15 5 (0 9)	
			1 15 (0 02)[d]		1 07 (0 01)[c]
60	R-thiopental	13 7 (0.9)[c]		15.8 (2.5)[a]	
	S-thiopental	16.9 (1 5)		17 3 (2 8)	
			1 22 (0 03)[d]		1.09 (0 01)[d]

Table 3 Mean (SEM) tissue.plasma distribution coefficients of thiopental enantiomers and their relevant enantiomer ratios in CNS and peripheral tissues in three groups ($n=6$) of rats after infusion with thiopental to a target plasma concentration of 40 µg ml^{-1} for 20 min R *vs* S and S/R *vs* 1· [a]*P*<0 05; [b]*P*<0 01; [c]*P*<0.005, [d]*P*<0.001, [e]*P*<0.0005

Tissue	Time (min)	R-thiopental	S-thiopental	S/R ratio
Cortex	20	0 86 (0.17)	0.73 (0 10)	0.88 (0 03)[a]
	30	1 08 (0.07)[b]	0.96 (0 07)	0.89 (0 02)[c]
	60	1.24 (0 10)[c]	1.03 (0 09)	0 83 (0.02)[d]
Striatum	20	0.92 (0.19)	0 74 (0.11)	0.84 (0 03)[c]
	30	1.12 (0.04)[c]	1.01 (0 05)	0 90 (0 02)[c]
	60	1.25 (0.07)[e]	1 02 (0.06)	0 82 (0.02)[c]
Hippocampus	20	0.95 (0.17)	0.79 (0.09)	0.87 (0 04)[a]
	30	1 02 (0 06)[a]	0.93 (0 05)	0.91 (0.03)[a]
	60	1 16 (0.07)[c]	1.01 (0 08)	0.87 (0 02)[c]
Cerebellum	20	0 97 (0.22)	0.81 (0.14)	0 87 (0 03)[b]
	30	1 14 (0 05)[d]	1 01 (0 06)	0.88 (0.02)[d]
	60	1 26 (0.08)[e]	1 05 (0.09)	0 83 (0 02)[e]
Brachial cord	20	1.21 (0.18)	1.02 (0 12)	0 86 (0 03)[c]
	30	1 44 (0.11)[c]	1.28 (0 10)	0.89 (0.02)[c]
	60	1 43 (0 11)[e]	1 16 (0.10)	0 81 (0 02)[e]
Sacral cord	20	1 15 (0 19)	0 96 (0 09)	0.86 (0 04)[a]
	30	1.44 (0.07)[c]	1.25 (0.09)	0 86 (0.02)[e]
	60	1 56 (0.18)[b]	1 28 (0 13)	0.83 (0 03)[c]
Muscle	20	0.39 (0.08)	0.33 (0.05)	0 89 (0.03)[a]
	30	0 73 (0.06)[a]	0.65 (0 06)	0 90 (0.02)[b]
	60	0 74 (0 09)[c]	0 63 (0.08)	0 85 (0.01)[e]
Fat	20	1 73 (0.32)	1.51 (0.21)	0 90 (0.04)
	30	3 69 (0.46)[e]	3.36 (0 44)	0.91 (0.01)[e]
	60	8.90 (0 81)[e]	7 57 (0 73)	0 85 (0 02)[e]

Table 4 Mean (SEM) tissue·plasma distribution coefficients based on expected plasma unbound concentrations of thiopental enantiomers and their relevant enantiomer ratios in CNS and peripheral tissues in three groups ($n=6$) of rats after infusion of thiopental to a target plasma concentration of 40 µg ml^{-1} for 20 min R *vs* S and S/R *vs* 1: [a]*P*<0.05; [b]*P*<0 01; [c]*P*<0 005, [d]*P*<0 001; [e]*P*<0 0005

Tissue	Time (min)	R-thiopental	S-thiopental	S/R ratio
Cortex	20	4 6 (0 9)	3 8 (0 5)	0 85 (0 03)[b]
	30	7 4 (0 5)[c]	6 2 (0.4)	0.83 (0 02)[e]
	60	7.9 (0.7)[d]	6.0 (0 5)	0.76 (0 02)[e]
Striatum	20	4.9 (1.0)	3 8 (0.6)	0 81 (0 03)[c]
	30	7 7 (0 3)[e]	6 5 (0.3)	0.84 (0 02)[e]
	60	7 9 (0 4)[e]	5.9 (0 4)	0.75 (0 01)[c]
Hippocampus	20	5.0 (0 9)	4 1 (0 5)	0.85 (0 04)[b]
	30	7.0 (0 4)[c]	6 0 (0 3)	0 85 (0 03)[c]
	60	7 4 (0 4)[e]	5 8 (0.5)	0 79 (0 02)[e]
Cerebellum	20	5 2 (1.2)	4 2 (0 7)	0 84 (0 03)[c]
	30	7.9 (0 4)[e]	6 5 (0 4)	0 82 (0 02)[c]
	60	8 0 (0 5)[e]	6 1 (0 5)	0 76 (0 02)[e]
Brachial cord	20	6 4 (1 0)[a]	5 3 (0 6)	0 83 (0 02)[c]
	30	9 9 (0 7)[d]	8 3 (0.6)	0.83 (0 02)[c]
	60	9 9 (1 1)[c]	7 4 (0 7)	0 76 (0 03)[e]
Sacral cord	20	6.1 (1 0)	4 9 (0 5)	0.84 (0 04)[b]
	30	10 0 (0.5)[e]	8 1 (0 6)	0 81 (0 02)[e]
	60	9.9 (1 1)[c]	7 4 (0.7)	0 76 (0 03)[e]
Muscle	20	2 1 (0 4)	1 7 (0 3)	0 86 (0 03)[b]
	30	5 0 (0.4)[c]	4 2 (0 4)	0 84 (0 02)[c]
	60	4 7 (0 6)[e]	3 6 (0 5)	0 78 (0 01)[e]
Fat	20	9.2 (1 7)	7 8 (1 1)	0 88 (0 04)[a]
	30	25 5 (3.2)[e]	21.6 (2 8)	0 85 (0 01)[e]
	60	56 3 (5.1)[e]	43.8 (4 2)	0 78 (0 01)[e]

when based on unbound plasma concentrations. Distribution coefficients for spinal regions were higher than for brain regions (*P*<0.01). The muscle:plasma distribution coefficient for R-thiopental was greater than that for S-thiopental at 30 (*P*<0.005) and 60 (*P*<0.0005) min, and the (S:R) thiopental enantiomer ratio of the distribution coefficients was lower at 60 than at 30 min (*P*<0.05). The fat:plasma distribution coefficients for R-thiopental were greater than those for S-thiopental at 30 (*P*<0.0005) and 60 (*P*<0.0005) min; the values for both enantiomers were higher at 60 than at 30 min (*P*<0.005). The (S:R) thiopental enantiomer ratio of distribution coefficients was lower at 60 than at 30 min (*P*<0.002).

Discussion

Our study has produced several interesting findings. First, there was no difference in the rates of equilibration of R- and S-thiopental between plasma and aECF in the striatum and hippocampus. Hence we found no evidence to support the notion that the enantiomeric differences in anaesthetic potency or the biphasic EEG response, as reported by others,[1,2] is associated with enantiomericdifferences in rates of equilibration between plasma and brain. Furthermore, the actual rate of attaining plasma–brain aECF equilibration was surprisingly slow, thereby contrasting with published data on the rate of equilibration between EEG signal variables and arterial plasma thiopental concentrations,[1] and with the clinical observation of rapid induction of thiopental anaesthesia. Second, enantioselectivity was found in plasma concentrations and in tissue:plasma distribution coefficients. Third, tissue:plasma distribution coefficients of both enantiomers were time-sensitive, even in highly perfused CNS tissues.

Plasma–brain equilibration

Using microdialysis, the ECF surrounding the probe tip can be sampled repetitively, allowing the local kinetics of solutes to be defined. Solute microdialysate concentrations are accepted as equivalent to aECF concentrations after the *in vivo* recovery for a given set of experimental conditions has been incorporated.[6–9 13 14 17] Both striatal and hippocampal regions were sampled as both are putative target regions for thiopental EEG effects and are kinetically similar regarding its effects.[18–22] Thiopental has a rapid rate of entry into the brain because of its high lipophilicity; cerebral uptake is a function of cerebral blood flow, the plasma–brain ECF concentration gradient of its unbound unionized form and its apparent volume of distribution in the brain.[23–27] The first measured aECF concentration in this study (at 2.5 min) demonstrated that uptake of thiopental into the striatum and hippocampus was rapid, given the measured lag time and diffusional delay. aECF concentrations, however, were surprisingly low.

In this study, rats were anaesthetized within about 30 s of commencing the infusion of thiopental. However, the slow increase in aECF thiopental concentrations observed over the duration of the infusion seems inconsistent with rapid induction of thiopental anaesthesia. It is also inconsistent with the reported equilibration rate constant between arterial plasma and the EEG effect site (in rats approximately 80 s) and with the constancy of the plasma concentration–effect relationship for thiopental.[1 2 27]

Moreover, aECF concentrations should reflect unbound plasma thiopental concentrations but these were found not to converge (within experimental error) until 10 min after the infusion had finished. These findings may reflect a limitation of microdialysis application to tracking the large-influx of highly lipophilic drugs, such as thiopental, that can rapidly diffuse between plasma and lipid-rich CNS tissue. It was noted that in previous analogous kinetic studies using this technique, the drugs used were less lipophilic with relatively longer equilibration times.[8 9 14] A possible explanation is that the local (and competitive) rate of thiopental uptake into brain parenchyma exceeded the rate of diffusion into the microdialysis probe. Had the infusion continued until steady-state, brain aECF thiopental concentrations should have reached a limiting value equivalent to unbound plasma concentrations. At the end of the infusion, however, thiopental redistribution from the brain parenchyma back into plasma would have begun thus maintaining nearly constant aECF concentrations during the post-infusion period, despite plasma and brain tissue concentrations declining to approximately 60% of those present at 20 min. By 60 min, the unbound total concentration of thiopental in plasma was estimated to be about 4.4 μg ml^{-1}, a value similar to the aECF concentration at 60 min (3.4 μg ml^{-1}). The discrepancy probably reflects a difference in unbound drug concentration under the conditions of the experiment from the value measured by equilibrium dialysis and indicates the need for incorporation of albumin (or other relevant protein) into the perfusion medium for studying very lipophilic and/or highly plasma protein bound substances.

Enantioselectivity in plasma and tissue concentrations

In rats from study 1, the (S:R) ratio of thiopental enantiomer plasma concentrations increased throughout the study. This is consistent with the higher total body clearance of R-thiopental, as reported in other species,[5 15] and in our ongoing studies in rats.[28] In the hippocampal group, where the sample size was larger, significant enantiomeric bias was also apparent in aECF concentrations such that S-thiopental was greater than R-thiopental over the duration of sampling. The ratios of aECF:plasma thiopental AUC values from the 2.5-min fraction interval were significantly higher in the striatum group than in the hippocampus group. Measurement of CNS regional blood flows in rats, by uptake of iodo[^{14}C]antipyrine, found flow rates of 1.37±0.07 and 1.15±0.08 ml g^{-1} min^{-1} in the striatum and hippocampus, respectively,[29] suggesting that the initially higher uptake into the striatum may be a result of its higher regional blood flow. The lack of a significant difference between aECF thiopental concentrations in the striatum and hippocampus, when compared over the entire infusion period, is consistent with regional blood flows decreasing towards a common basal value.[29 30 31]

Tissue concentrations and distribution coefficients

Preferential tissue distribution of R-thiopental was found. Indeed, the (S:R) ratio of tissue:plasma distribution coefficients for thiopental enantiomers, which was <1 when derived from total plasma concentrations, decreased further when derived from unbound plasma concentrations. By 30 and 60 min, CNS tissue concentrations of both enantiomers decreased from those at 20 min, whereas little change occurred in muscle concentrations, and the fat concentrations of both enantiomers increased substantially. This finding is consistent with the traditional view of consecutive redistribution of thiopental from well perfused CNS tissue to less well perfused tissue. However, concurrently, the CNS tissue:plasma distribution coefficients for each thiopental enantiomer tended to increase, albeit disproportionally (R>S), as demonstrated by the significant decrease in their (S:R) ratio between 30 and 60 min. Hence tissue enantioselectivity was not uniform. These findings indicate that caution needs to be applied when incorporating distribution coefficients into physiologically based pharmacokinetic models.

In summary, although we found enantioselectivity in the pharmacokinetics of thiopental, there was no pharmacokinetic evidence to support differences in CNS potency between the thiopental enantiomers being a result of differences in their rates of equilibration across the blood–brain barrier. Our ongoing studies suggest that differences in potency may be accounted for largely by differences in intrinsic efficacy at the GABA$_A$ receptor.[32]

Acknowledgements

The study was funded in part by the Australian and New Zealand College of Anaesthetists, the Ramaciotti Foundation and the National Health and Medical Research Council of Australia

References

1 Ebling WF, Danhof M, Stanski DR Pharmacodynamic characterization of the electroencephalographic effects of thiopental in rats. *J Pharmacokinet Biopharm* 1991; **19**: 123–43

2 Gustafsson LL, Ebling WF, Osaki E, Stanski DR. Quantitation of depth of thiopental anesthesia in the rat. *Anesthesiology* 1996; **84**. 415–27

3 Huang LM, Barker JL. Pentobarbital. stereospecific actions of (+) and (–) isomers revealed on cultured mammalian neurons. *Science* 1980; **207**: 195–7

4 Downes H, Perry RS, Ostlund RE, Karler R A study of the excitatory effects of barbiturates. *J Pharmacol Exp Ther* 1970; **175**: 692–9

5 Mather LE, Upton RN, Huang JL, Ludbrook GL, Gray E, Grant C. The systemic and cerebral kinetics of thiopental in sheep: enantiomeric analysis. *J Pharmacol Exp Ther* 1996; **279**: 291–7

6 Benveniste H. Brain microdialysis. *J Neurochem* 1989; **52**: 1667–79

7 Ungerstedt U. Microdialysis—principles and applications for studies in animals and man *J Int Med* 1991: **230**: 365–73

8 Elmquist WF, Sawchuk RJ. Application of microdialysis in pharmacokinetic studies. *Pharm Res* 1997, **14**: 267–8

9 Stahl L The use of microdialysis in pharmacokinetics and pharmacodynamics. In: Robinson TE, Justice JB. *Microdialysis in the Neurosciences* Amsterdam: Elsevier Science, 1991; 155–74

10 Gustafsson LL, Ebling WF, Osaki E, *et al.* Plasma concentration clamping in the rat using a computer-controlled infusion pump. *Pharm Res* 1992, **9**. 800–7

11 Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates.* Sydney: Academic Press, 1986

12 Wang W, Wong SL, Sawchuk RJ. Microdialysis calibration using retrodialysis and zero-net flux: application to a study of the distribution of zidovudine to rabbit cerebrospinal fluid and thalamus. *Pharm Res* 1993; **10**: 1411–19

13 Dykstra KH, Hsiao JK, Morrison PF, *et al.* Quantitative examination of tissue concentration profiles associated with microdialysis. *J Neurochem* 1992; **58**: 931–40

14 Lindfors N, Amberg G, Ungerstedt U. Intracerebral microdialysis: experimental studies of diffusion kinetics. *J Pharmacol Methods* 1989; **22**: 141–56

15 Cordato DJ, Gross AS, Herkes GK, Mather LE. Pharmacokinetics of thiopentone enantiomers following intravenous injection or prolonged infusion of rac-thiopentone. *Br J Clin Pharmacol* 1997, **43**: 355–62

16 Huang JL, Mather LE, Duke CC. High-performance liquid chromatographic determination of thiopentone enantiomers in sheep plasma. *J Chromatogr B* 1995; **673**· 245–50

17 Parsons LH, Justice JB. Quantitative approaches to in vivo brain microdialysis. *Crit Rev Neurobiol* 1994; **8**: 189–220

18 Keita H, Lecharny JB, Henzel D, Desmonts JM, Mantz J. Is inhibition of dopamine uptake relevant to the hypnotic action of i.v. anaesthetics? *Br J Anaesth* 1996; **77**: 254–6.

19 Lecharny J-B, Salord F, Henzel D, Desmonts J-M, Mantz J Effects of thiopental, halothane and isoflurane on the calcium-dependent and -independent release of GABA from striatal synaptosomes in the rat. *Brain Res* 1995; **670**. 308–12

20 Archer DP, Roth SH. Pharmacodynamics of thiopentone Nocifensive reflex threshold changes correlate with hippocampal electroencephalography. *Br J Anaesth* 1997; **79**: 744–9

21 MacIver MB, Mandema JW, Stanski DR, Bland BH. Thiopental uncouples hippocampal and cortical synchronized electroencephalographic activity. *Anesthesiology* 1996; **84**: 1411–24

22 Mantz J, Varlet C, Lecharny JB, Henzel D, Lenot P, Desmonts J-M. Effects of volatile anesthetics, thiopental, and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. *Anesthesiology* 1994; **80** 352–63

23 Crawford JS. Speculation: the significance of varying the mode of injection of a drug with special reference to the brain and the placenta. *Br J Anaesth* 1966; **38**· 628–40

24 Goldstein A, Aronow K, Kalman SM. *Principles of Drug Action: the Basis Of Pharmacology*, 2nd Edn. New York: Wiley, 1974, 129–217

25 Igari Y, Sugiyama Y, Awazu S, Hanano M. Comparative physiologically based pharmacokinetics of hexobarbital, phenobarbital, and thiopental in the rat. *J Pharmacokinet Biopharm* 1982, **10**· 53–75

26 Upton RN, Ludbrook GL, Grant C, Gray EC. In vivo relationships between the cerebral pharmacokinetics and pharmacodynamics of thiopentone in sheep after short-term administration *J Pharmacokinet Biopharm* 1996, **24**: 1–18

27 Buhrer M, Maitre PO, Hung OR, Ebling WF, Shafer SL, Stanski DR. Thiopental pharmacodynamics I. Defining the pseudo-steady-state serum concentration–EEG effect relationship. *Anesthesiology* 1992; **77**: 226–36

28 Mather LE, Edwards SR, Duke CC, Cousins MJ. Enantioselectivity of thiopental distribution into central neural tissue of rats· an interaction with halothane. *Anesth Analg* 1999, **89**· 230–5

29 Sakurada O, Kennedy C, Jehle J, Brown JD, Carbin GL, Sokoloff L. Measurement of local cerebral blood flow with iodo[^{14}C]antipyrine. *Am J Physiol* 1978; **3**· H59–66

30 Goldman H, Sapirstein LA. Brain blood flow in the conscious and anesthetized rat. *Am J Physiol* 1973; **224**· 122–6

31 Wada DR, Harashima H, Ebling WF, Osaki EW, Stanski DR. Effects of thiopental on regional blood flows in the rat. *Anesthesiology* 1996; **84**: 596–604

32 Cordato D, Chebib M, Mather LE, Herkes GK, Johnston GAR Stereoselective interaction of R-(+)-thiopentone and S-(–)-thiopentone enantiomers with the GABA$_A$ receptor. *Br J Pharmacol* 1999 **128**: 77–82

British Journal of Anaesthesia 84 (1). 74–86 (2000)

BJA

REVIEW ARTICLE

Gastrointestinal luminal P_{CO_2} tonometry: an update on physiology, methodology and clinical applications

J. J. Kolkman[1], J. A. Otte[1] and A. B. J. Groeneveld[2]*

[1]Department of Gastroenterology, Medisch Spectrum Twente, Enschede, The Netherlands. [2]The Medical Intensive Care Unit, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

*Corresponding author

Br J Anaesth 2000; 84: 74–86

Keywords: gastrointestinal tract, pH; gastrointestinal tract, mucosal perfusion; measurement techniques, tonometry; partial pressure, carbon dioxide; carbon dioxide, partial pressure

Gastrointestinal mucosal pH (pHi), calculated from tonometrically measured P_{CO_2} in the gastrointestinal lumen and blood bicarbonate content using the Henderson–Hasselbalch equation, has been suggested to constitute an index of the adequacy of splanchnic mucosal perfusion. This may relate to the prognosis of critically ill patients, as bowel wall hypoperfusion may result in tissue injury, increased permeability, endotoxin–bacterial translocation and a harmful inflammatory (cytokine) response.[11 12 26 30 37 54 61 68 71 73 98 106 114 122 130 131] The theory is that hypoperfusion below a critical level causes tissue (mucosal) carbon dioxide accumulation and acidosis. As carbon dioxide diffuses easily across membranes, the P_{CO_2} in the gut lumen also increases, leading to widening of the tonometer–blood P_{CO_2} gradient. In fact, pHi has been used successfully to guide treatment and to improve the outcome of critically ill patients.[36 46 49 61 68] Nevertheless, tonometry has not yet become a routine intensive care monitoring technique. This may relate to uncertainties regarding its physiological background, methodology and clinical usefulness.[46] This review will therefore update current thoughts on these aspects.[36 46]

Physiological background

Gastrointestinal hypoperfusion

Several conditions may lead to altered gut perfusion (Table 1). Haemorrhagic hypotension, cardiac tamponade, cardiac bypass or vasopressin infusion for example, may lead to mucosal hypoperfusion along the entire gastrointestinal tract, and this may be assessed with the help of simultaneous tonometric measurements in various gastrointestinal segments.[1 82 84 101 117 118 134] In fact, the bowel P_{CO_2} gradient may increase and pHi decrease during hypoperfusion states, similar to changes in gastrically determined tonometric variables. This may also apply to sepsis and shock, even if the oxygen demands by the bowel wall increase,[101] and to cardiopulmonary bypass surgery, during which bowel wall oxygen demands may decrease following hypothermia and increase during rewarming.[3 11 29 53 106 110 111 129] Moreover, shock may result in early selective splanchnic vasoconstriction so that gastric tonometry may reveal an early indicator of general hypoperfusion.[33 36 46 55 101 134] The gastric tonometric P_{CO_2} gradient proved an early, sensitive indicator of hypovolaemia during haemorrhage in healthy volunteers.[55] An increase in the gastric P_{CO_2} gradient and decrease in pHi during general hypoperfusion in humans may relate to angiotensin II-induced selective splanchnic vasoconstriction.[67 109]

Experimental studies using vascular occlusion and reperfusion, induction of shock or pharmacological splanchnic vasoconstriction have revealed that changes in blood flow to the gut wall, as measured by microspheres, laser Doppler, electromagnetic or ultrasonic flow probes, or reflectance spectrophotometry, were paralleled by concordant changes in tonometric variables.[2 57 70 73 82 84 101 108 115 117–119 125 131 134] A decrease in blood flow to less than 50% of baseline during incremental hypoperfusion leads to an increased tonometric P_{CO_2} relative to supplying (and draining) blood values. This results in a decrease in pHi, in parallel with the decreasing blood flow and decrease in tissue P_{O_2} and oxygen consumption.[1 2 13 36 46 50 55 57 73 82 84 101 103 108 115 117–119 125 134] This may result in tissue damage and increased mucosal permeability.[1 11 12 26 71 73 106 122 131] In critically ill, septic and mechanically ventilated patients, laser Doppler (and reflectance spectroscopy) measurement of gastric mucosal blood flow, hepatosplanchnic blood flow measured by indocyanine green, or hepatic breakdown of injected lidocaine to monoethylglycinexylidide, were lower in

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Conditions in which tonometry is of potential clinical value

Perioperative monitoring in major surgery, including cardiopulmonary bypass, major (emergency) vascular surgery and liver transplantation
Myocardial infarction and shock
Heart failure
Pulmonary embolism and shock
Traumatic/hypovolaemic shock
Sepsis and shock
Pericardial tamponade
Fluid and drug therapy for shock
Infusion of vasopressin or other vasoconstrictors
Acute pancreatitis
Mesenteric thrombosis
Necrotizing enterocolitis
Ischaemic colitis
Bowel obstruction
Chronic coeliac and mesenteric vascular disease
Assessment of bowel viability
Intolerance to tube feeding
Weaning from mechanical ventilation
Haemodialysis

patients with an increased P_{CO_2} gradient and subnormal pHi than in those without these tonometric abnormalities, or in healthy controls.[35 93 102 127] In fact, drug-induced changes in blood flow assessed by these techniques can be paralleled by concordant changes in P_{CO_2} gradient and pHi.[34 93 101 102 127]

However, tonometric variables are indicators of the blood flow to demand ratio. Changes in splanchnic blood flow, as assessed by indocyanine green clearance or laser Doppler techniques, are not necessarily accompanied by changes in tonometric variables and vice versa, particularly when demand changes, for example with the variation in body temperature associated with cardiopulmonary bypass surgery and sepsis. During hypothermic cardiopulmonary bypass surgery, gastric mucosal (Doppler) blood flow may decrease, but neither the gastric luminal to blood P_{CO_2} gradient nor pHi may change.[3 106 114] The generally observed decrease in pHi during rewarming and in the postoperative phase may not concord with splanchnic blood flow changes and oxygen consumption, which may even increase, and this discrepancy suggests either increased oxygen demand or insufficient ability of pHi to reflect the balance between oxygen supply and demand.[53 106 109 110 114 129] Even during normothermic cardiopulmonary bypass surgery, bowel demands may increase and may be insufficiently met by an increase in blood flow, thereby lowering pHi.[53] Disconcordant changes in cardiac output and gut blood flow on the one hand and tonometric variables on the other during treatment with catecholamines, with an increase in the former but no improvement in the latter, may relate in part to redistribution of blood flow within the stomach or gut wall, away from the mucosa.[11 110 111 127 129] During endotoxaemic–septic shock, gut blood flow may not decrease and gut P_{O_2} and oxygen consumption may increase, but this may not prevent a subnormal gastrointestinal pHi developing, suggesting redistribution of blood flow, impaired oxygen use, or both.[131] Finally, it remains to be seen if deterioration in tissue oxygenation and increased anaerobic metabolism through severe hypoxaemia or anaemia also result in tonometry changes[70] as it is conceivable that a high blood flow but insufficient oxygen delivery may limit the increase in P_{CO_2} and decrease in pHi.[3]

Sublingual, oesophageal, gastric and bowel P_{CO_2} tonometry

Luminal production of carbon dioxide during buffering of gastric acid by bicarbonate or bacterial fermentation may limit the specificity of luminal P_{CO_2} and thus pHi as indicators of the adequacy of mucosal perfusion in the stomach and large bowel, respectively. This may not occur with tonometry in the oesophagus or sublingually as these areas are not supplied by splanchnic blood vessels Thus the sensitivity of tonometry for early detection of general hypoperfusion may be inferior to that for detecting hypoperfusion in the stomach or small bowel, where selective vasoconstriction may occur.[33] During severe haemorrhage or sepsis in animals, sublingual, oesophageal and gastric P_{CO_2} nevertheless increased in parallel and simultaneously with the decrease in blood flow and increase in blood lactate concentration.[52 64 100 118 124] With regard to the value of small bowel *vs* gastric tonometry, widening of the tonometer–blood P_{CO_2} gradient in pigs may be earlier in the small bowel than in the stomach during haemorrhagic shock,[101] but not during cardiac tamponade.[1] The increase in jejunal P_{CO_2} during endotoxaemia in horses was less and occurred later than that of gastric P_{CO_2}.[123] Walley and colleagues,[134] however, showed that during haemorrhagic hypotension, widening of the tonometer–blood P_{CO_2} gradient was less and less variable in the jejunum than in the stomach, largely because of greater measurement error in the latter.

P_{CO_2} gradient vs pHi as an indicator of mucosal hypoperfusion

It has been argued repeatedly that pHi is a composite variable, consisting of a systemic and locally derived variable, and should be replaced by the tonometer–blood P_{CO_2} (or perhaps pH) gradient. This is especially so if tonometry is being done to yield a sensitive and specific measure of the adequacy of gastrointestinal mucosal perfusion, independent of systemic metabolic and respiratory alterations.[26 42 46 51 55 61–64 73 87 120 134] Indeed, the major pitfall in the calculation of pHi from gastric P_{CO_2} and arterial bicarbonate content is the assumption that the latter equals mucosal content. In humans, the mucous layer of the acid-secreting stomach also contains bicarbonate, which is secreted by non-parietal cells and helps to protect the underlying mucosa from the gastric acid secreted by parietal cells.[69] Mild hypovolaemia in human volunteers decreases gastric bicarbonate secretion more than acid secretion, and this may be associated with alterations in tissue bicarbonate concentration.[69] Hence the bicarbonate content of the mucosa may normally be higher than in blood, while hypoperfusion may result in a dissimilar decrease in blood and mucosal bicarbonate content, depending on the balance between general and regional hypoperfusion, diminished bicarbonate secretion and the degree of buffering of lactic acid in the hypoperfused stomach wall.[73,115,119,125] Conversely, changes in arterial blood bicarbonate content may lead to alterations in calculated pHi, independent of changes in the degree of mucosal hypoperfusion and the increase in P_{CO_2} gradient.[120] I.v. bicarbonate administration to a patient with mesenteric thrombosis resulted in an increase in gastric tonometer pHi to normal values, despite a necrotic bowel found at laparotomy, but the stomach may not have represented the small bowel.[10] Conversely, in cardiac surgery patients, a rapid decrease in arterial bicarbonate content by volume loading during surgery may contribute to a lowered gastric pHi, independent of luminal P_{CO_2}.[6]

Moreover, gastric P_{CO_2} closely parallels local arterial (and draining venous) blood P_{CO_2} values during changes in alveolar ventilation, as demonstrated in animals and human volunteers with (presumably) normal perfusion, so that changes in pHi may result from changes in alveolar ventilation, independent of mucosal hypoperfusion.[13,27,31,79,117] Conversely, changes in alveolar ventilation in patients undergoing mechanical ventilation resulted in changes in tonometric variables similar to blood P_{CO_2}, if gastric mucosal blood flow remained adequate.[13,31] The dependency of pHi on arterial blood bicarbonate content and P_{CO_2} may underlie the observed concurrent changes or correlations between calculated pHi on the one hand and arterial blood pH and acid–base variables, including lactate concentration, on the other.[19,31,41,49,61,83,135]

It is still unclear as to the threshold for anaerobic metabolism, but the upper limit of a normal gradient would be approximately 1.2 kPa.[79,87,115,126] The increased luminal P_{CO_2} during hypoperfusion is assumed to stem from two sources. With a moderately gradual reduction in perfusion, mucosal P_{CO_2} accumulates after a reduced washout and an increase in tissue and venous P_{CO_2}. A further decrease in blood flow results in a steep increase in tissue (luminal) and to a lesser extent venous P_{CO_2} and this may be caused by buffering of anaerobically produced lactate and protons by mucosal bicarbonate.[57,73,115,119,134] Hence a gradient between tissue and draining venous P_{CO_2}, in spite of allegedly high diffusibility of carbon dioxide, may be a marker of anaerobic tissue metabolism. It seems that a decrease in tissue oxygen consumption and tension and development of anaerobic metabolism and production of lactic acid occurs at a P_{CO_2} gradient of 3.3 kPa or greater, a value that can be regarded as the critical gradient.[2,36,115,119,134] A lower gradient, however, does not exclude a focal oxygen deficit in the mucosa.[79] The baseline P_{CO_2} tonometer–blood gradient in patients with gastric erosions or ulcerations and stenotic or occluded coeliac and mesenteric vessels at angiography was approximately 0.4 kPa and increased to 2.5 kPa during submaximal exercise, whereas no such increase was observed in patients with normal angiography.[80] Thus some patients had lesions in the stomach attributable to hypoperfusion in spite of a resting P_{CO_2} gradient presumably below the critical value of approximately 3.3 kPa.[80] The lesions may relate to intermittent or patchy hypoperfusion rendering the mucosa susceptible to damage by other factors.

Methodological considerations

Comparison of tonometric with directly measured variables

In the control state, tonometric pHi may agree with directly measured tissue pH in the stomach and bowel.[38] Some authors have shown that directly measured P_{CO_2} is higher than tonometrically derived P_{CO_2}, and that the response time of the latter is slower.[36,103] This may result in tonometric pHi overestimating directly measured tissue pH during sudden hypoperfusion.[2,36] The latter may also relate to the erroneous bicarbonate assumption discussed above.

Normal values

Normal values for gastric tonometry have been defined, taking *in vivo* determined correction factors and blood-gas analyser bias (see below) into account.[79] The upper limit of normal values for P_{CO_2} was 6.5 kPa and for the tonometer–blood P_{CO_2} gradient, 1.2 kPa, so that tonometric P_{CO_2} is normally a few kPa higher than that in the blood supply. The lower limit of normal for pHi is 7.33 and for the pH gradient, −0.06.[79] This agrees in part with other reports, where the upper limit of normal pH varied between 7.32 and 7.35.[12,19,30,35,49,59,60,65,68,79,83,89,98,99,108,126] Data on normal P_{CO_2} or the P_{CO_2} gradient in the human gut are lacking. Bass and colleagues noted that the control intestinal (jejunal or ileal) mass spectrometer P_{CO_2} was 11.9 kPa in dogs, but arterial values were not given.[9] The normal fibreoptic/tonometric ileum to blood P_{CO_2} gradient may, as in the stomach, amount to 1.3–2.7 kPa in pigs and dogs.[73,82,101,115,119] The normal oesophagus to blood P_{CO_2} gradient is also in that range.[52,82] There is no information on the normal tonometer balloon equilibration characteristics from the oesophagus to the large bowel, where changes in luminal contents and diffusion conditions may have an effect.

Gastric P_{CO_2} as a measure of gastrointestinal mucosal P_{CO_2}

It is generally assumed that rapid diffusion results in luminal P_{CO_2} being identical to mucosal P_{CO_2}. Nevertheless, the increase in tonometric P_{CO_2} may underestimate that of directly measured P_{CO_2}.[39,103] Carbon dioxide diffuses rapidly from mucosa into the lumen with complete equilibration in 60 min, while diffusion in the opposite direction is about four times slower.[38] Even though carbonic anhydrase, present in the gastric mucosa, may contribute to the difference in diffusion rate, inhibition of carbonic anhydrase activity did not decrease the rate of P_{CO_2} build-up in the tonometer balloon.[76] This suggests that the balloon P_{CO_2} arises from gastric contents as opposed to the gastric mucosa. Indeed, gastric carbon dioxide content may decrease by 6% and P_{CO_2} may decrease by 0.3 kPa during equilibration of 1.5 ml of tonometer balloon saline, in the absence of transmucosal diffusion.[76] Gastric balloon rather than transmucosal carbon dioxide diffusion may be the rate limiting step during gastric P_{CO_2} tonometry.[76]

Gastric secretion of acid

The close approximation of luminal and mucosal P_{CO_2} may be lost in the stomach when carbon dioxide is produced by buffering of gastric acid, contributing to a relatively poor reproducibility of gastric pHi.[134] Indeed, in the normally perfused upper gastrointestinal tract, luminal P_{CO_2} may directly relate to the amount of acid secreted and buffered in the stomach,[105 116] and has even been used as a measure of gastric acid secretion.[105 116] This luminally produced carbon dioxide stems from the buffering of gastric acid by bicarbonate secreted by the gastric mucosa[105] or by bicarbonate entering the stomach through duodenal reflux or from saliva via the oesophagus. The increase in P_{CO_2} resulting from buffering can be prevented by inhibition of acid secretion.[38 105] Hence it has been recommended to perform tonometry after H_2 block of gastric acid secretion.[36 46] In fact, gastric P_{CO_2} in human volunteers is 1.3–2.7 kPa above blood levels and decreases towards arterial levels with less interindividual variation after inhibition of acid secretion by the H_2 blocker ranitidine, so that calculated pHi is higher in the presence of prior H_2 block.[75 112 126] When duodenogastric reflux is simulated by oral administration of bicarbonate in an amount approximating the hourly pancreaticoduodenal production, gastric P_{CO_2} increases to approximately 10.7 kPa above blood levels but only in the absence and not in the presence of prior H_2 block.[75] Removal of gastric acid by suction may not decrease gastric P_{CO_2} towards blood values.[112] This can be explained by the fact that gastric acid, which is produced in the deep pits of the gastric mucosa, is buffered by gastric bicarbonate in the mucus layer covering these pits.[75] Buffering of gastric acid by administration of non-carbon dioxide releasing antacids such as aluminium oxide–magnesium hydroxide also releases large amounts of carbon dioxide *in vitro* and is therefore not useful.[132]

It can be questioned whether data in healthy subjects would apply to critically ill patients as H_2 blockers, which would be expected to lower P_{CO_2}, had no effect on gastric P_{CO_2} in the seriously ill.[22] Together with the concept that inhibition of acid secretion may predispose to gastric bacterial colonization and nosocomial infections, this may be the reason that many authors do not use H_2 block before tonometry in critically ill patients.[17 31 34 109–111 121 129] Similarly, administration of sucralfate, which has acid-buffering capacities and increases gastric bicarbonate secretion, and could therefore be expected to increase P_{CO_2} in the presence of acid, had no effect on P_{CO_2} in critically ill patients.[21] This may be explained by a reduction in gastric acid secretion, as shown by a relatively high gastric juice pH that fails to decrease after pentagastrin infusion in many critically ill patients after operation.[6 44 60] During the first 24 h after cardiopulmonary bypass surgery, gastric fluid may be acidic (pH <4.0) in a minority of patients.[6] Simulation of duodenogastric reflux by gastric bicarbonate administration had no effect on gastric P_{CO_2} immediately after surgery, indicating lack of gastric acid secretion but increased gastric P_{CO_2}, on the first postoperative day by 2.7 kPa in six of 10 subjects.[6] The observations suggest postoperative recovery occurs after reduced gastric acid secretion caused by transient hypoperfusion.

Indeed, gastric acid secretion is an active, energy-demanding process.[69] During haemorrhagic hypotension, gastric mucosal blood flow and gastric acid (and bicarbonate) secretion diminish, but less so in pentagastrin- or histamine-stimulated conditions than in animals pretreated with H_2 blockers.[69] This suggests that gastric acid secretion in shock is blood flow dependent and that administration of H_2 blockers (or proton pump inhibitors) may further diminish energy-demanding gastric acid secretion and blood flow and may protect against the development of stress ulcers related to hypoperfusion.[66 69 92] In fact, a low pHi may be associated with failure to acidify the gastric lumen in response to pentagastrin[60] The combination of a reduced demand and an increased perfusion reserve during inhibition of acid secretion probably results in lowered sensitivity of tonometry as an indicator of early perfusion failure or gastric mucosal hypoperfusion. A patient who develops an increased P_{CO_2} gradient might either have mucosal hypoperfusion or recurrence of gastric acid secretion after amelioration of hypoperfusion. Inhibition of acid secretion reduces the incidence of this dilemma, thereby increasing the validity of gastric tonometry, and simple measurement of gastric juice pH, preferably by continuous monitoring, could solve the problem. An aspirated juice pH above 4.0–5.0, checked with the help of litmus paper, would suggest minimum or no buffering effects,[6 76 85 126] so that changes in gastric P_{CO_2} would probably result from changes in mucosal perfusion only.

However, H_2 blockers such as ranitidine may fail to control gastric juice pH, even in critically ill patients[97] The efficacy of the first dose after i v. administration is reduced within 24 h,[95] and after 48 h, the gastric juice pH is again less than 4.0 for 60% of the time.[44] The proton pump inhibitor omeprazole increases gastric juice pH more efficiently and continuously than H_2 antagonists, even 24 h after administration.[95] While abolishing acid and inhibiting bicarbonate secretion, the drug may maintain mucosal perfusion, in contrast with H_2 blockers that decrease both acid secretion and mucosal blood flow.[92] Preserved blood flow after proton pump inhibitors may contribute to preventing stress ulcer bleeding during haemorrhagic hypotension.[66]

Tonometry in fed or fasting state?

Eating a meal might serve as a stress test for mucosal vasodilator reserve as the meal stimulates gastric acid secretion, and small bowel secretions, and active resorption of nutrients. The increased energy expenditure of the gut causes an increase in blood flow to both the stomach and small gut mucosa.[84] Indeed, luminal P_{CO_2} may increase to 53.5 kPa in the normal stomach and duodenum after gastric feeding, as a result of buffering of the increased acid by the increased bicarbonate output.[116] As the increased postprandial P_{CO_2} is caused by acid buffering, it might be expected that acid suppression could circumvent this increase. However, although H_2 antagonists can effectively block basal or fasting acid secretion, suppression of meal-stimulated gastric acid secretion may be incomplete, even in critically ill patients.[97] Even in the presence of H_2 blockers, gastric feeding of critically ill patients may increase gastric P_{CO_2} relative to blood values, presumably as a consequence of the production of carbon dioxide.[75 90] This may also occur in some individuals where acid secretion has been inhibited completely by a combination of ranitidine and the muscarinic receptor antagonist pirenzepine.[77 97] The cause of this increase proved to be the buffering of amino acid-containing food by gastroduodenal bicarbonate.[77 90] P_{CO_2} may also decrease shortly after gastric feeding because of dilution. Hence the volume of food given and the gastric emptying rate determine this dilutional effect.[77] Finally, when the reserve in cardiac output is limited, a meal may increase blood flow in the proximal gastrointestinal tract while diminishing blood flow and pHi in the distal gastrointestinal tract.[84] Hence normal tonometry variables after a meal do not exclude gastrointestinal hypoperfusion. Taken together, it is recommended to perform gastric tonometry in the fasting state as this may increase specificity, even though it may decrease the sensitivity of the method.[36 46 47 77 90] Alternatively, duodenal feeding may affect gastric tonometry less than gastric feeding.

Confounding factors

In the colon, carbon dioxide production by bacteria may lead to a lower normal pHi than in the stomach.[12 37] Indeed, normal colonic P_{CO_2} may amount to 40.0 kPa, depending on the diet.[20] In horses, who have a large bacterial flora and eat almost exclusively carbohydrates, the normal colonic P_{CO_2} was >26.7 kPa.[123] These observations should prompt collection of data for normal values of colonic P_{CO_2} or the effects of bowel preparation, laxatives or antibiotics, as sigmoid tonometry has been reported to be of value in aortic surgery patients.

Entry of environmental air into the stomach may transiently lower gastric P_{CO_2}.[20] Hence a negative gradient may indicate a measurement artefact. This occurs particularly in non-intubated, spontaneously breathing patients.

Sources of error during manual fluid tonometry

Manual fluid (usually saline) P_{CO_2} tonometry is laborious and involves seven steps, each carrying a risk of error so that reproducibility may be relatively poor (Table 2).[28 134] The steps are: (1) infusion of exactly 2.5 ml in the catheter, (2) waiting a fixed dwell time to allow for (partial) equilibration with surrounding luminal P_{CO_2} (in most studies 30 min), (3) withdrawing and discarding the first 1.0 ml representing catheter deadspace, (4) aspiration of the final 1.5 ml into a syringe, capping it and storage on ice, (5) sending the capped syringe to the laboratory for analysis in the blood-gas analyser without delay and (6) calculation of steady-state P_{CO_2} using a correction factor for each dwell time that is less than that needed for full equilibration (Fig. 1). With the help of P_{CO_2}, arterial blood bicarbonate content and the Henderson–Hasselbalch equation, a regional, mucosal pH (pHi) can be calculated. It is likely that the sources of error involved in manual fluid tonometry have limited its widescale clinical application.[28 46]

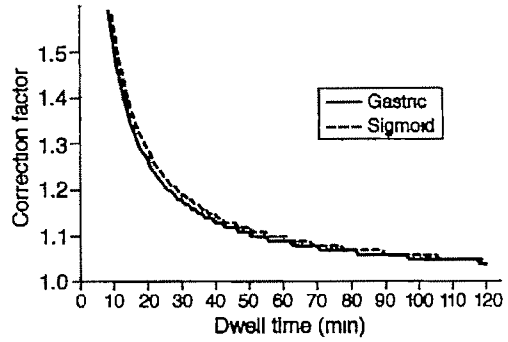


Fig 1 Manual saline tonometry. the correction factor is obtained for use in calculating steady-state P_{CO_2} from measured P_{CO_2} when a dwell time is used which is less than that needed for full equilibration. Gastric- and sigmoid-type tonometers are shown

Catheter deadspace

With each tonometer measurement, the balloon fluid is aspirated and measured in a blood-gas analyser. However, as the volume of the tonometer tube itself is approximately 1.0 ml, the last 1 ml from the balloon resides in this deadspace. With a new measurement, this 1.0 ml deadspace volume is then pushed into the balloon and mixed with freshly infused fluid. Thus the P_{CO_2} in the balloon at the start of the dwell time is variable and depends partly on the last measured P_{CO_2}. We found that with dwell times of 10 and 20 min, this phenomenon may cause errors in measured P_{CO_2} of 10% and 6%, respectively, at a deadspace P_{CO_2} of 4.0 kPa. At longer dwell times this error becomes negligible.[124] The deadspace error can be avoided either by a calculation based on the last measured P_{CO_2} and the dwell time or by flushing the tonometer four times with fresh saline to remove all remaining, carbon dioxide-containing saline in the catheter deadspace, thus ensuring a P_{CO_2} of 0 kPa in the tonometer balloon before each subsequent measurement.[124] Errors associated with an unrecognized deadspace effect may have influenced the manufacturer's correction factors for short dwell times.

Table 2 Sources of error associated with manual fluid tonometry

Problem	Result	Solution
Blood-gas analyser bias	Error, dependent on fluid and analyser	Evaluate and correct
Measurement error	*In vitro* 3%, *in vivo* 6–8%	–
Poor anaerobic technique	Decrease in P_{CO_2} of 8%	Careful anaerobic technique
Improper storage of syringe	Decrease in P_{CO_2} after 60 min of at least 8%	No delay before analysis
Imprecise dwell time	Error	Instructions and training, or using dwell times >60 min
Deadspace contamination	Error of 6–10% at 10 or 20 min dwell times	Rinse tonometer four times before fluid installation
Incorrect correction factors	Error	Use correct correction factors

Table 3 Blood-gas analyser bias for P_{CO_2} measurements in saline Bias=Percentage difference from true P_{CO_2} at a P_{CO_2} of approximately 5.3 kPa

Manufacturer	First author and source	Bias
Radiometer		
ABL2	Knichwitz, *Anaesthesia* 1995	−10
ABL3	Temmesfeld, *Intensive Care Medicine* 1997	−12
ABL130	Knichwitz, *Anaesthesia* 1995	−12
ABL300	Riddington, *Critical Care Medicine* 1994	−18
ABL330	Temmesfeld, *Intensive Care Medicine* 1997	−7
ABL505	Knichwitz, *Anaesthesia* 1995	−6
ABL520	Takala, *Critical Care Medicine* 1994	−6
ABL620	Venkatesh, *Anaesthesia and Intensive Care* 1998	−20
Ciba-Corning		
Ciba238	Takala, *Critical Care Medicine* 1994	−5
Ciba278	Kolkman, *Intensive Care Medicine* 1997	−15
Ciba288	Knichwitz, *Anaesthesia* 1995	−29
Ciba840	Kolkman, *Intensive Care Medicine* 1997	−11
Instrumentation Laboratories		
IL1302	Takala, *Critical Care Medicine* 1994	−8
Novastat		
Nova4	Takala, *Critical Care Medicine* 1994	−26
Nova5	Temmesfeld, *Intensive Care Medicine* 1997	−46
Nova7	Riddington, *Critical Care Medicine* 1994	−49
Nova9	Knichwitz, *Anaesthesia* 1995	−57
Eschweiler	Knichwitz, *Anaesthesia* 1995	−51

Blood-gas analyser bias and dwell time-dependent correction factors

It has become apparent that blood-gas analysers, calibrated for blood or calibration fluid, may underestimate P_{CO_2} measured in saline (or air) by 5–50%.[72 79 81 113 128] The magnitude of the error depends on the fluid and blood-gas analyser used, and potentially on the absolute P_{CO_2}.[72 81 113 128] The mean error among analysers (at P_{CO_2} 40 torr) is 12%, ranging from 5% to 29% (Table 3). Consequently, other fluids have been evaluated and used, including succinylated gelatin,[8 81 113] albumin,[72] Hartmann's solution,[113] phosphate–bicarbonate[81] and phosphate or citrate buffer.[3 72 81 127 128] Buffered solutions, including succinylated gelatin,[113] may have the advantage over non-buffered solutions that the conversion of carbon dioxide to bicarbonate in the buffer decreases the propensity for accidental losses to the environment, either via incompletely aerobic techniques or during processing in the blood-gas analyser. Their use may thus result in less bias and greater precision and reproducibility than for P_{CO_2} measurement in non-buffered solutions.[72 81 128] Indeed, the error in P_{CO_2} measurements in saline and phosphate was approximately 7% after careless syringe handling or after 1 h storage of capped syringes.[81] Measurement bias and handling errors could be reduced to approximately 3% with the use of succinylated gelatin and phosphate–bicarbonate buffer.[81] However, buffered solutions increase the time needed for P_{CO_2} to equilibrate by a factor of 2–5.[81 128] Non-bicarbonate-based buffered solutions could share some of the advantages without these disadvantages. Indeed, saline and phosphate had similar P_{CO_2} build-up kinetics and similar propensity for accidental errors, while the bias for phosphate was smaller.[72 81 128] Nevertheless, saline and phosphate may be equally suitable as a tonometer fluid provided strict anaerobic techniques are used and the blood-gas analyser bias is known and taken into account.[72 81]

It is hard to assess the manufacturer's correction factors[37] as *in vitro* studies from which they have been derived have not been published and the role of the deadspace effect and blood-gas analyser bias has not been taken into account. Blood-gas analyser bias has evoked debates in the literature[74 112] on the issue of whether a correction for the bias should be superimposed on the correction for incomplete equilibration provided in the manufacturer's correction factors.[37] Compared with the manufacturer's correction factors, the correction factors for short dwell times were considerably larger because we avoided the deadspace effect by repeated flushing of the tonometer.[79] However, the difference at long dwell times cannot be explained by these effects and must be attributed to blood-gas analyser bias incorporated in the manufacturer's correction factors.[74 79] Indeed, the manufacturer's correction factors for dwell times beyond 90 min are large. But we have shown that after a 120 min dwell time, the tonometer P_{CO_2} is 96% of the surrounding value (Fig. 1) with a corresponding correction factor of 1.03 compared with 1.17 advised by the manufacturer.[79] That this 1.17 does not relate to incomplete diffusion can be appreciated from a study by Fiddian-Green and colleagues documenting the same P_{CO_2} after dwell times of 60 and 360 min.[37] In fact, correction for both incomplete equilibration using the factors supplied by the manufacturer and blood-gas analyser bias may result in overestimations of P_{CO_2} while incomplete correction may result in underestimations.[58 63 79]

In vitro corrections factors have been assumed to apply to the *in vivo* situation.[27] However, in comparing P_{CO_2} equilibration kinetics of tonometers placed in a saline bath and in the stomach of healthy volunteers, the rate of P_{CO_2} equilibration in the latter proved 31% slower.[79] This may relate to gastric juice, gastric folds and mucus covering the tonometer balloon *in vivo*. Finally, the rate of P_{CO_2} build-up depends on the size and diameter of the catheter, because of the sink effect of the deadspace.[124] Hence equilibration may be a few percent slower when using a long, sigmoid-type catheter instead of the shorter gastric type. This is relevant at 10-min dwell times only.[124] When the sources of error are taken into account, manual measurements are not only reproducible but accurate.[79] The response of the fluid technique, however, remains relatively slow.

Temperature corrections

As with blood P_{CO_2} and acid–base balance, it is unclear if tonometer fluid P_{CO_2} and pHi should be corrected for body temperature if it is not 37°C, for example during hypothermia or fever, as the correction on the blood-gas machine may yield unpredictable results.[8 29 63] Nevertheless, it seems prudent to calculate the P_{CO_2} blood–tonometer fluid gradient from measurements made at the same temperature.

Air and others types of tonometry

From animal and human (post-cardiac surgery) studies,[117] it has been suggested that P_{CO_2} determination in gastric air or juice would represent mucosal P_{CO_2} and could replace the balloon tonometry technique. The balloon technique facilitates and standardizes gastric sampling, and air as opposed to saline tonometry allows more rapid diffusion and thus a shorter response time.[128]

The recently introduced semi-continuous automated air tonometry involves a pump which automatically inflates (and deflates) via an airtight circuit, 6–8 ml of air into the tonometer balloon every 5–60 min (standard 10 min). This measures P_{CO_2} in the aspirated air using a modified infrared capnograph and may eliminate some of the sources of measurement error of manual fluid tonometry, thereby increasing the clinical applicability of the technique.[8 27 58 63 80 126 128] The device is available commercially (Tonocap, Datex, Finland). The response time of the Tonocap, defined as the time needed to reach a 95% change in P_{CO_2} at dwell times of 5–10 min, was 10–18 min. Bias was +1% to −3% and precision about 1%.[27 58 80 128] The relatively long response time, particularly at a high P_{CO_2} and in comparison with the dwell time, may relate to a deadspace effect. P_{CO_2} measurements by the air tonometry technique may underestimate (high) saline tonometric P_{CO_2}, even if they are highly correlated.[27 58 63 79 117] This may relate to 'overcorrection' of the latter. Air tonometry may also overestimate saline tonometry, possibly as a consequence of the use of wrong correction factors for the saline technique.[8 27] The techniques may have some methodological problems and sources of error in common. This may relate, in part, to the probable need for fasting and inhibition of gastric acid secretion and the value of pHi *vs* the tonometer–blood P_{CO_2} gradient. The accuracy of P_{CO_2} measured by air tonometry is not influenced by temperature corrections.[8]

Capnometric recirculating gas tonometry involves a tonometer with two lumina, connected to a circulation pump and an infrared sensor, yielding P_{CO_2} measurements which correlate highly with those obtained by the manual saline technique.[50–52] Compared with the latter, recirculating gas tonometry has a more rapid response time (5 min), allows online measurements and is more sensitive during haemorrhage and endotoxaemia.[50–52] A new method involves a fibreoptic P_{CO_2} sensor which also allows monitoring of pH and P_{O_2}.[73] The sensor proved faster and more accurate than saline tonometry, both *in vitro* and *in vivo*. The potential for using this probe nasogastrically needs further study. Other techniques that may become available for direct mucosal P_{CO_2} measurements include the ion-sensitive field effect transistor sensor.[100 103 118 125] Finally, the tonometry can also be used to measure gastrointestinal luminal nitric oxide concentrations.[1]

Clinical applications

Diagnostic aid in symptomatic coeliac and mesenteric vascular disease

Some patients with otherwise unexplained abdominal signs of dyspepsia and pain (abdominal angina) may have chronic gastrointestinal vascular disease, but it is hard to establish a relation between signs and symptoms on the one hand and objective indicators of gastrointestinal hypoperfusion, such as abnormal angiographic findings, on the other.[80] The management of these patients and the effect of reconstructive vascular surgery may be hard to predict. A diagnostic test for gastrointestinal hypoperfusion that also predicts the success of surgery is therefore needed.[80 84] It has been suggested that gastric tonometry during a test meal may be used.[16 39] However, feeding may confound tonometry in the stomach and may thereby yield negative results, even in patients with otherwise proven splanchnic hypoperfusion.[43 75] Alternatively, during exercise, perfusion of the splanchnic organs is at risk because of the 'steal' effect of the increased blood flow to skeletal muscle. Hence vascular disease in the splanchnic region and diminished vasodilator reserve could increase the risk of hypoperfusion during exercise. Indeed, many patients with presumed gastrointestinal vascular disease may have abdominal complaints on exercise. We therefore assessed the value of exercise gastric tonometry in managing patients with suspected gastrointestinal hypoperfusion.[78] When the patients were divided on the basis of normal angiograms and those with stenotic lesions in the coeliac or superior mesenteric artery, the P_{CO_2} gradient during exercise did not increase in the former but increased to about 2.7 kPa in the latter group, with only a minority of patients exhibiting a supranormal gradient at rest. Furthermore, the exercise tonometric findings correlated with a symptom score, the extent of angiographic abnormalities and the presence of discrete mucosal lesions on gastroscopy, consistent with mucosal hypoperfusion and damage. In some patients re-examined after reconstructive surgery, the exercise tonometry test had normalized.[78] Gastric tonometry could help to diagnose acute mesenteric vascular disease resulting in bowel hypoperfusion and necrosis, provided that the stomach is also partly involved and some tissue metabolism remains.[10 73 117]

Estimating prognosis from pHi or the P_{CO_2} gradient and pHi in critically ill patients

The conditions wherein (gastric) tonometric variables proved prognostically significant for the development of multiple organ failure and subsequent death are: orthotopic liver transplantation[135]; acute pancreatitis[17]; cardiopulmonary bypass and other types of major, emergency vascular surgery[29 30 41 54 94 98 114]; sepsis; trauma[25 26 49 61 65 68 83]; and mechanical ventilation.[31 59 93 96] Furthermore, an increased P_{CO_2} gradient and a low pHi were predictive of failure to wean mechanically ventilated patients, independently of arterial blood and ventilatory variables, presumably because of splanchnic diversion of blood flow to exercising respiratory muscles with an increased workload.[18 31 96]

The fact that tonometric P_{CO_2} depends partly on arterial P_{CO_2}, and that the bicarbonate content is shared between arterial pH and calculated pHi, may explain the correlation observed between arterial pH and pHi, and the approximate similar predictive value of both indices.[19 23 41 45] Although splanchnic hypoperfusion and lactate production may influence the systemic indicators, tonometric variables may nevertheless correlate only poorly with systemic factors.[40 48] As hyperlactataemia-associated metabolic acidosis is prognostically unfavourable in critically ill patients, it can be questioned if tonometry is of additive predictive value.[4 19 48 59 62 65 83] A low (subnormal) pHi or increased P_{CO_2} gradient may be superior or have additive value in the prediction of morbidity, that is multiple organ failure and mortality, to global haemodynamic and metabolic variables, including lactate concentration and acid–base variables in the systemic blood of critically ill patients.[25 26 32 40 42 56 59 61 68 83 93 94 96 98] A subnormal gastric pHi may predict circulating markers of an inflammatory response and a poor outcome with postoperative complications and multiple organ failure after major cardiac, vascular and abdominal surgery.[30 62 98] After cardiopulmonary bypass surgery, however, neither pHi nor the P_{CO_2} gradient in the stomach may constitute an early predictor of increased permeability, endotoxaemia and death in the ICU, whereas global haemodynamics and systemic lactate concentration may predict a worsening disease course.[5 14 54 114]

Even though P_{CO_2} or pH gradients may be more specific indicators of gastric hypoperfusion than pHi, it may be questioned if the former are equally useful prognostic variables as pHi, which incorporates a systemic variable.[25 26 40 42 45 59 61 68 93] In recent studies in critically ill patients, pHi, but not pH or P_{CO_2} gradients, proved prognostic indicators,[45 59] suggesting an additive value of systemic acid–base disorders in predicting outcome. In addition, a low pHi may predict occurrence of stress ulcer bleeding and ischaemic colitis when measured in the stomach and sigmoid colon of critically ill patients.[12 37 71 122 130] Hence, pHi may be superior to the P_{CO_2} gradient in predicting stress ulcer (bleeding) in the stomach, as the development of stress ulcers may not only relate to local factors but also to systemic acidosis.[69] In fact, lowering of the blood bicarbonate content is a risk factor and systemic alkalinization protects against stress ulcer development during haemorrhagic shock and mucosal hypoperfusion in animals.[69] Taken together, it emerges that the components of pHi, P_{CO_2} as a measure of alveolar ventilation and gastric hypoperfusion, and bicarbonate concentration, as a measure of general circulatory status, are of varying importance in different patients and disease stages.

Children

In a study in paediatric patients with sepsis, lactate content, but not pHi or P_{CO_2} gradients, predicted outcome, suggesting the superiority of systemic over regional abnormalities.[32] In contrast, in many other studies in critically ill (septic) children, pHi and P_{CO_2} (or pH) gradients were better predictors than systemic haemodynamic and metabolic variables, including blood pH, bicarbonate and lactate concentrations, for haemodynamic complications, multiple organ failure and survival.[23 24 31 32 56 83]

Sigmoid colon

Even though the appropriate methodology of sigmoid tonometry has still to be established, studies have suggested that the technique may be helpful in predicting tissue hypoxia and injury leading to ischaemic colitis, the main cause of morbidity and mortality after major abdominal vascular surgery.[12 37 71 122 130] Colonic hypoperfusion detected by tonometry may be associated with endotoxaemia and cytokine release that might contribute to mortality.[122]

Gastric tonometry may also be of predictive value after (emergency) major vascular surgery.[12,88,94]

Effect of interventions

As a low gastric pHi or increased P_{CO_2} gradient may be prognostically important, studies have examined the effect of various interventions on these tonometric variables, but the beneficial effect on morbidity and mortality of 'pHi guided' treatment is still controversial.[7,49,104,108] A variety of treatment procedures consisting of fluid and drug therapy, such as dopamine, dopexamine, epinephrine and norepinephrine, aimed at restoration of splanchnic blood flow, have been evaluated after cardiopulmonary bypass surgery,[11,42,99,110,111,129] trauma and sepsis.[15,48,49,68,86,87,101,102,107,121,127] Colloid fluids may be superior to crystalloids but different types may differ in their ability to increase global oxygen delivery and uptake, and to ameliorate a low gastric pHi in septic and postoperative patients.[15,91] Some catecholamine treatments in haemodynamically compromised patients may benefit the splanchnic circulation and others may not, as judged by a decrease in gastric P_{CO_2}, an increase in pHi, or both, in a variety of conditions.[7,11,42,48,86,87,91,102,107,110,121,127,129] For example, norepinephrine and dobutamine decreased the (elevated) gastric P_{CO_2} gradient and increased (subnormal) pHi. Dopamine, dopexamine or epinephrine treatment had no effect or tended to further decrease pHi in the treatment of sepsis and shock, even if systemic haemodynamics were unchanged or improved.[48,86,87,91,102,127] Dopexamine or dobutamine treatment may not prevent a decrease in pHi during and after cardiopulmonary bypass surgery, even if they increase systemic and hepatosplanchnic blood flow and oxygen delivery.[11,42,110,129] In other critically ill patients, dopexamine appeared to improve splanchnic blood flow and a subnormal pHi, independent of systemic haemodynamics, suggesting selective splanchnic vasodilatation, while dopamine had no such effect.[121]

Vasodilator therapy by infusion or inhalation of prostacyclin may improve hepatosplanchnic blood flow and decrease the tonometric gastric P_{CO_2} gradient during septic shock.[34] Administration of nitroprusside or angiotensin converting enzyme (ACE) inhibitors did not change the gastric P_{CO_2} gradient or pHi after cardiac surgery and this argues against a role for angiotensin in splanchnic vasoconstriction, although in this study the baseline P_{CO_2} gradient was not markedly increased.[109,111] ACE inhibition may ameliorate an increased P_{CO_2} gradient and a low pHi in trauma, however, even if systemic haemodynamic variables do not change.[67] Pulsatile blood flow may better preserve gastric mucosal perfusion adequacy than non-pulsatile flow during cardiopulmonary bypass.[41] Inducing muscle paralysis in mechanically ventilated patients may increase a reduced pHi, suggesting redistribution of blood flow from respiratory to splanchnic organs.[89] Treatment of sepsis and trauma patients with antioxidants may prevent a decrease in oxygen extraction abilities and gastric pHi, particularly during transient hyperoxia.[7] During large intestinal surgery, gastric P_{CO_2} increased relative to blood values, independent of global haemodynamics; adjunctive clonidine administration did not attenuate this increase.[133] Abdominal decompression in trauma-related intra-abdominal hypertension may normalize a low pHi, particularly in patients who survive.[62]

Conclusion

Gastrointestinal tonometry of the luminal to blood P_{CO_2} gradient can be used to assess the adequacy of mucosal perfusion provided that, if applied to the empty stomach, acid buffering and carbon dioxide generation are avoided. Appropriate use may improve the accuracy of manual fluid tonometry until the semi-continuous automated air tonometry technique, which may eliminate some sources of error inherent to the manual technique, becomes widely available. This may broaden the clinical applicability of gastrointestinal luminal tonometry as a monitoring tool in a variety of conditions.

References

1 Åneman A, Snygg J, Pettersson A, Johansson B, Holm M, Fandriks L. Detecting gastrointestinal hypoperfusion during cardiac tamponade in pigs: a role for nitric oxide tonometry? *Crit Care Med* 1998; **26**: 1251–7

2 Antonsson JB, Haglund UH. Gut intramucosal pH and intraluminal P_{O_2} in a porcine model of peritonitis or haemorrhage. *Gut* 1995; **37**: 791–7

3 Bacher A, Mayer N, Rajek AM, Haider W. Acute normovolaemic haemodilution does not aggravate gastric mucosal acidosis during cardiac surgery. *Intensive Care Med* 1998; **24**: 313–21

4 Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest* 1991; **99**: 956–62

5 Bams JJ, Kolkman JJ, Roukens MP, *et al.* Reliable gastric tonometry after coronary surgery: need for acid suppression despite transient failure of acid secretion. *Intensive Care Med* 1998; **24**: 1139–43

6 Bams J, Mariani M, Groeneveld A. Predicting outcome after cardiac surgery: comparison of global haemodynamic and tonometric variables. *Br J Anaesth* 1999; **41**. 33–7

7 Barquist E, Kirton O, Windsor J, *et al.* The impact of antioxidant and splanchnic-directed therapy on persistent uncorrected gastric mucosal pH in the critically injured trauma patient. *J Trauma* 1998; **44**: 355–60

8 Barry B, Mallick A, Hartley G, Bodenham A, Vucevic M. Comparison of air tonometry with gastric tonometry using saline and other equilibrating fluids: an *in vivo* and *in vitro* study. *Intensive Care Med* 1998; **24**: 777–84

9 Bass BL, Schweitzer EJ, Harmon JW, Kraimer J. Intraluminal pCO_2: a reliable indicator of intestinal ischemia. *J Surg Res* 1985; **39**: 351–60

10 Benjamin E, Polokoff E, Oropello JM, Leibowitz AB, Iberti TJ. Sodium bicarbonate administration affects the diagnostic accuracy of gastrointestinal tonometry in acute mesenteric ischemia. *Crit Care Med* 1992; **20**: 1181–3

11 Berendes E, Mollhoff T, Van Aken H, *et al.* Effects of dopexamine on creatinine clearance, systemic inflammation, and splanchnic oxygenation in patients undergoing coronary artery bypass grafting. *Anesth Analg* 1997; **84**: 950–7

12 Bjorck M, Hedberg B. Early detection of major complications

after abdominal aortic surgery. predictive value of sigmoid colon and gastric intramucosal pH monitoring. *Br J Surg* 1994; **81**: 25–30

13 Boda D, Muranyi L. 'Gastrotonometry'. An aid to the control of ventilation during artificial respiration. *Lancet* 1959; **1**: 181–2

14 Bohrer H, Schmidt H, Motsch J, Gust R, Bach A, Martin E. Gastric intramucosal pH: a predictor of survival in cardiac surgery patients with low cardiac output? *J Cardiothorac Vasc Anesth* 1997, **11**: 184–6

15 Boldt J, Heesen M, Muller M, Pabsdorf M, Hempelmann G. The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. *Anesth Analg* 1996; **83**. 254–61

16 Boley SJ, Brandt LJ, Veith FJ, Kosches D, Sales C. A new provocative test for chronic mesenteric ischemia *Am J Gastroenterol* 1991; **86**: 888–91

17 Bonham MJ, Abu-Zidan FM, Simovic MO, Windsor JA. Gastric intramucosal pH predicts death in severe acute pancreatitis. *Br J Surg* 1997; **84**: 1670–4

18 Bouachour G, Guiraud MP, Gouello JP, Roy PM, Alquier P. Gastric intramucosal pH: an indicator of weaning outcome from mechanical ventilation in COPD patients. *Eur Respir J* 1996; **9**: 1868–73

19 Boyd O, Mackay CJ, Lamb G, Bland JM, Grounds RM, Bennett ED. Comparison of clinical information gained from routine blood-gas analysis and from gastric tonometry for intramural pH *Lancet* 1993; **341**: 142–6

20 Calloway D. Gas in the alimentary canal. In: Code C, ed *Handbook of Physiology, Section 6: Alimentary Canal*. Washington DC: American Physiological Society, 1968; 2839–59

21 Calvet X, Baigorri F, Duarte M, *et al.* Effect of sucralfate on gastric intramucosal pH in critically ill patients *Intensive Care Med* 1997; **23**: 738–42

22 Calvet X, Baigorri F, Duarte M, *et al.* Effect of ranitidine on gastric intramucosal pH in critically ill patients *Intensive Care Med* 1998; **24**: 12–17

23 Calvo C, Ruza F, Lopez-Herce J, Dorao P, Arribas N, Alvarado F Usefulness of gastric intramucosal pH for monitoring hemodynamic complications in critically ill children *Intensive Care Med* 1997; **23**: 1268–74

24 Casado-Flores J, Mora E, Perez-Corral F, Martinez-Azagra A, Garcia-Teresa MA, Ruiz-Lopez MJ. Prognostic value of gastric intramucosal pH in critically ill children. *Crit Care Med* 1998, **26**: 1123–1127

25 Chang MC, Meredith JW. Cardiac preload, splanchnic perfusion, and their relationship during resuscitation in trauma patients. *J Trauma* 1997, **42**: 577–82

26 Charpentier C, Audibert G, Dousset B, *et al.* Is endotoxin and cytokine release related to a decrease in gastric intramucosal pH after hemorrhagic shock? *Intensive Care Med* 1997; **23**: 1040–8

27 Creteur J, De Backer D, Vincent JL Monitoring gastric mucosal carbon dioxide pressure using gas tonometry: *in vitro* and *in vivo* validation studies. *Anesthesiology* 1997, **87**: 504–10

28 Crispin C, Jones W, Daffurn K. How consistently do RNs perform the procedure of collecting specimens for measurement of gastric pHi and CO_2? *Intensive Crit Care Nurs* 1995; **11** 123–5

29 Croughwell ND, Newman MF, Lowry E, *et al* Effect of temperature during cardiopulmonary bypass on gastric mucosal perfusion. *Br J Anaesth* 1997; **78**: 34–8

30 Donati A, Battisti D, Recchioni A, *et al.* Predictive value of interleukin 6 (IL-6), interleukin 8 (IL-8) and gastric intramucosal pH (pH-i) in major abdominal surgery *Intensive Care Med* 1998; **24**. 329–35

31 Duke T, Butt W, South M, Shann F. The Dco_2 measured by gastric tonometry predicts survival in children receiving extracorporeal life support. Comparison with other hemodynamic and biochemical information. Royal Children's Hospital ECMO Nursing Team. *Chest* 1997; **111**: 174–9

32 Duke TD, Butt W, South M. Predictors of mortality and multiple organ failure in children with sepsis. *Intensive Care Med* 1997; **23**: 684–92

33 Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogeneous regional vascular responses to simulated transient hypovolemia in man. *Intensive Care Med* 1994; **20**: 414–20

34 Eichelbronner O, Reinelt H, Wiedeck H, *et al* Aerosolized prostacyclin and inhaled nitric oxide in septic shock: different effects on splanchnic oxygenation? *Intensive Care Med* 1996, **22**: 880–7

35 Elizalde JI, Hernandez C, Llach J, *et al* Gastric intramucosal acidosis in mechanically ventilated patients. role of mucosal blood flow. *Crit Care Med* 1998, **26**: 827–32

36 Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *Br J Anaesth* 1995; **74**: 591–606

37 Fiddian-Green RG, Amelin PM, Herrmann JB, *et al.* Prediction of the development of sigmoid ischemia on the day of aortic operations Indirect measurements of intramural pH in the colon. *Arch Surg* 1986; **121**: 654–60

38 Fiddian-Green RG, Pittenger G, Whitehouse WM Back-diffusion of CO_2 and its influence on the intramural pH in gastric mucosa *J Surg Res* 1982; **33**: 39–48

39 Fiddian-Green RG, Stanley JC, Nostrant T, Phillips D Chronic gastric ischemia, a cause of abdominal pain or bleeding identified from the presence of gastric mucosal acidosis. *J Cardiovasc Surg* 1989, **30**: 852–9

40 Friedman G, Berlot G, Kahn RJ, Vincent JL Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis *Crit Care Med* 1995, **23**: 1184–93

41 Gaer JA, Shaw AD, Wild R, *et al.* Effect of cardiopulmonary bypass on gastrointestinal perfusion and function. *Ann Thorac Surg* 1994; **57**: 371–5

42 Gardeback M, Settergren G, Ohquist G, Tiren C Effect of dopexamine on calculated low gastric intramucosal pH following valve replacement *Acta Anaesthesiol Scand* 1995, **39**. 599–604

43 Geelkerken RH, Schultze Kool LJ, Hermans J, Zarza MT, Van Bockel JH Chronic splanchnic ischaemia. Is tonometry a useful test? *Eur J Surg* 1997; **163**: 115–21

44 Geus WP, Smith SJ, De Haas JA, Lamers CB Pattern of 72-hour intragastric acidity in a homogeneous group of intensive care unit patients *Dig Dis Sci* 1994; **39**. 1608–12

45 Gomersall CD, Joynt GM, Ho KM, Young RJ, Buckley TA, Oh TE. Gastric tonometry and prediction of outcome in the critically ill. Arterial to intramucosal pH gradient and carbon dioxide gradient. *Anaesthesia* 1997; **52**: 619–23

46 Groeneveld AB, Kolkman JJ. Splanchnic tonometry. a review of physiology, methodology, and clinical applications *J Crit Care* 1994, **9**: 198–210

47 Groeneveld ABJ, Vervloet MG, Kolkman JJ. Gastric tonometry in the fed or fasting state? *Crit Care Med* 1998, **26**: 1937–40

48 Gutierrez G, Clark C, Brown SD, Price K, Ortiz L, Nelson C Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. *Am J Respir Crit Care Med* 1994, **150** 324–9

49 Gutierrez G, Palizas F, Doglio G, *et al.* Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 1992, **339**: 195–9

50 Guzman JA, Kruse JA. Continuous assessment of gastric intramucosal $P\mathrm{co}_2$ and pH in hemorrhagic shock using

capnometric recirculating gas tonometry. *Crit Care Med* 1997; **25**: 533–7

51 Guzman JA, Kruse JA. Gastric intramucosal P_{CO_2} as a quantitative indicator of the degree of acute hemorrhage. *J Crit Care* 1998; **13**: 49–54

52 Guzman JA, Lacoma FJ, Kruse JA. Gastric and esophageal intramucosal P_{CO_2} ($PiCO_2$) during endotoxemia: assessment of raw $PiCO_2$ and P_{CO_2} gradients as indicators of hypoperfusion in a canine model of septic shock. *Chest* 1998; **113**: 1078–83

53 Haisjackl M, Birnbaum J, Redlin M, *et al.* Splanchnic oxygen transport and lactate metabolism during normothermic cardiopulmonary bypass in humans. *Anesth Analg* 1998; **86**: 22–7

54 Hamilton-Davies C, Barclay GR, Cardigan RA, *et al.* Relationship between preoperative endotoxin immune status, gut perfusion, and outcome from cardiac valve replacement surgery. *Chest* 1997; **112**: 1189–96

55 Hamilton-Davies C, Mythen MG, Salmon JB, Jacobson D, Shukla A, Webb AR. Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 1997; **23**: 276–81

56 Hatherill M, Tibby SM, Evans R, Murdoch IA. Gastric tonometry in septic shock. *Arch Dis Child* 1998; **78**. 155–8

57 Heino A, Hartikainen J, Merasto ME, Alhava E, Takala J. Systemic and regional pCO_2 gradients as markers of intestinal ischaemia. *Intensive Care Med* 1998; **24**: 599–604

58 Heinonen PO, Jousela IT, Blomqvist KT, Takkunen OS. Validation of air tonometric measurement of gastric regional concentrations of CO_2 in critically ill septic patients. *Intensive Care Med* 1997; **23**: 524–9

59 Hernandez C, el Ebiary M, Gonzalez J, De la Bellacasa JP, Monton C, Torres A. Relationship between ventilator-associated pneumonia and intramucosal gastric pHi: a case-control study. *J Crit Care* 1996; **11**: 122–8

60 Higgins D, Mythen MG, Webb AR. Low intramucosal pH is associated with failure to acidify the gastric lumen in response to pentagastrin. *Intensive Care Med* 1994; **20**. 105–8

61 Ivatury RR, Simon RJ, Islam S, Fueg A, Rohman M, Stahl WM. A prospective randomized study of end points of resuscitation after major trauma: global oxygen transport indices versus organ-specific gastric mucosal pH. *J Am Coll Surg* 1996; **183**: 145–54

62 Ivatury RR, Porter JM, Simon RJ, Islam S, John R, Stahl WM. Intra-abdominal hypertension after life-threatening penetrating abdominal trauma: prophylaxis, incidence, and clinical relevance to gastric mucosal pH and abdominal compartment syndrome. *J Trauma* 1998; **44**: 1016–21

63 Janssens U, Graf J, Koch K, Hanrath P. Gastric tonometry: *in vivo* comparison of saline and air tonometry in patients with cardiogenic shock. *Br J Anaesth* 1998; **81**: 676–80

64 Jin X, Weil MH, Sun S, Tang W, Bisera J, Mason EJ. Decreases in organ blood flows associated with increases in sublingual P_{CO_2} during hemorrhagic shock. *J Appl Physiol* 1998; **85**: 2360–4

65 Joynt GM, Lipman J, Gomersall CD, Tan I, Scribante J. Gastric intramucosal pH and blood lactate in severe sepsis. *Anaesthesia* 1997; **52**: 726–32

66 Kawano S, Tanimura H, Sato N, *et al.* Effects of proton pump inhibitor on gastric mucosa hemodynamics and tissue oxygenation in anesthetized rats. *Eur J Pharmacol* 1992; **211**: 55–60

67 Kincaid EH, Miller PR, Meredith JW, Chang MC. Enalaprilat improves gut perfusion in critically injured patients. *Shock* 1998; **9**: 79–83

68 Kirton OC, Windsor J, Wedderburn R, *et al.* Failure of splanchnic resuscitation in the acutely injured trauma patient correlates with multiple organ system failure and length of stay in the ICU. *Chest* 1998; **113**: 1064–9

69 Kivilaakso E, Kiviluoto T, Mustonen H, Paimela H. Gastric mucosal acid–base balance. *J Intern Med* 1990; **732**. 63–68

70 Kleen M, Habler O, Hutter J, *et al.* Effects of hemodilution on gastric regional perfusion and intramucosal pH. *Am J Physiol* 1996; **271**: H1849–55

71 Klok T, Moll FL, Leusink JA, Theunissen DJ, Gerrits CM, Keijer C. The relationship between sigmoidal intramucosal pH and intestinal arterial occlusion during aortic reconstructive surgery. *Eur J Vasc Endovasc Surg* 1996; **11**: 304–7

72 Knichwitz G, Kuhmann M, Brodner G, Mertes N, Goeters C, Brussel T. Gastric tonometry: precision and reliability are improved by a phosphate buffered solution. *Crit Care Med* 1996; **24**: 512–16

73 Knichwitz G, Rotker J, Mollhoff T, Richter KD, Brussel T. Continuous intramucosal P_{CO_2} measurement allows the early detection of intestinal malperfusion. *Crit Care Med* 1998; **26**: 1550–7

74 Kolkman JJ, Groeneveld AB. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Med* 1997; **23**: 132

75 Kolkman JJ, Groeneveld AB, Meuwissen SGM. Effect of ranitidine on basal and bicarbonate enhanced intragastric P_{CO_2}: a tonometric study. *Gut* 1994; **35**: 737–41

76 Kolkman JJ, Groeneveld AB, Meuwissen SGM. Gastric P_{CO_2} tonometry is independent of carbonic anhydrase inhibition. *Dig Dis Sci* 1997; **42**: 99–102

77 Kolkman JJ, Groeneveld ABJ, Meuwissen SGM. Effect of gastric feeding on intragastric P_{CO_2} tonometry in healthy volunteers. *J Crit Care* 1999, **14**: 34–8

78 Kolkman JJ, Groeneveld ABJ, Van der Berg FG, Rauwerda JA, Meuwissen SGM. Gastric P_{CO_2} tonometry during exercise: a promising diagnostic tool for gastrointestinal ischaemia. *Gut* 1999; **44**: 163–7

79 Kolkman JJ, Steverink P, Groeneveld ABJ, Meuwissen SGM. Characteristics of time-dependent P_{CO_2} tonometry in the normal human stomach. *Br J Anaesth* 1998, **81**· 669–75

80 Kolkman JJ, Zwarekant LJ, Boshuizen K, Groeneveld ABJ, Meuwissen SGM. *In vitro* evaluation of intragastric P_{CO_2} measurement by air tonometry. *J Clin Monit* 1997: **13**: 115–19

81 Kolkman JJ, Zwarekant LJ, Boshuizen K, Groeneveld AB, Steverink PJ, Meuwissen SGM. Type of solution and P_{CO_2} measurement errors during tonometry. *Intensive Care Med* 1997; **23**: 658–63

82 Korsback C. Tissue pO_2 and pCO_2 in the gastrointestinal tract and liver during intravenous vasopressin infusion An experimental study in pigs. *Acta Chir Scand* 1984; **150**: 593–7

83 Krafte-Jacobs B, Carver J, Wilkinson JD. Comparison of gastric intramucosal pH and standard perfusional measurements in pediatric septic shock. *Chest* 1995; **108**: 220–5

84 Larson MV, Ahlquist DA, Karlstrom L, Sarr MG. Intraluminal measurement of enteric mucosal perfusion: relationship to superior mesenteric artery flow during basal and postprandial states in the dog. *Surgery* 1994; **115**: 118–26

85 Levine RL, Fromm RE Jr, Mojtahedzadeh M, Baghaie AA, Opekun AR Jr. Equivalence of litmus paper and intragastric pH probes for intragastric pH monitoring in the intensive care unit. *Crit Care Med* 1994; **22**· 945–8

86 Levy B, Bollaert P-E, Charpentier C, *et al* Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med* 1997; **23**: 282–7

87 Levy B, Bollaert P-E, Lucchelli J-P, Sadoune L-O, Nace L, Larcan A. Dobutamine improves the adequacy of gastric mucosal perfusion in epinephrine-treated septic shock. *Crit Care Med* 1997; **25**: 1649–54

88 Marik PE, Iglesias J, Maini B. Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aortic aneurysm repair. *J Crit Care* 1997; **12**: 51–5

89 Marik PE, Kaufman D. The effects of neuromuscular paralysis on systemic and splanchnic oxygen utilization in mechanically ventilated patients. *Chest* 1996, **109**· 1038–42

90 Marik PE, Lorenzana A. Effect of tube feedings on the measurement of gastric intramucosal pH. *Crit Care Med* 1996, **24**· 1498–1500

91 Marik PE, Mohedin M The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA* 1994, **272**: 1354–7

92 Mattsson H, Larsson H. Effects of omeprazole on gastric mucosal blood flow in the conscious rat. *Scand J Gastroenterol* 1987; **22**: 491–8

93 Maynard ND, Bihari DJ, Dalton RN, Beale R, Smithies MN, Mason RC Liver function and splanchnic ischemia in critically ill patients. *Chest* 1997; **111**: 180–7

94 Maynard ND, Taylor PR, Mason RC, Bihari DJ. Gastric intramucosal pH predicts outcome after surgery for ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 1996; **11**. 201–6

95 Merki HS, Wilder-Smith CH. Do continuous infusions of omeprazole and ranitidine retain their effect with prolonged dosing? *Gastroenterology* 1994; **106** 60–4

96 Mohsenifar Z, Hay A, Hay J, Lewis MI, Koerner SK. Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. *Ann Intern Med* 1993; **119**: 794–8

97 More DG, Raper RF, Watson CJ, Shenfield GM. Combination therapy with ranitidine and pirenzepine for control of intragastric pH in the critically ill *Crit Care Med* 1985; **13**: 651–5

98 Mythen MG, Purdy G, Mackie IJ, McNally T, Webb AR, Machin SJ. Postoperative multiple organ dysfunction syndrome associated with gut mucosal hypoperfusion, increased neutrophil degranulation and C1-esterase inhibitor depletion. *Br J Anaesth* 1993; **71**: 858–63

99 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**. 423–9

100 Nakagawa Y, Weil MH, Tang W, *et al.* Sublingual capnometry for diagnosis and quantitation of circulatory shock *Am J Respir Crit Care Med* 1998, **157**· 1838–43

101 Neviere R, Chagnon JL, Vallet B, *et al.* Dobutamine improves gastrointestinal mucosal blood flow in a porcine model of endotoxic shock *Crit Care Med* 1997; **25**: 1371–7

102 Neviere R, Mathieu D, Chagnon JL, Lebleu N, Wattel F The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med* 1996, **154**: 1684–8

103 Noc M, Weil MH, Sun S, Gazmuri RJ, Tang W, Pakula JL. Comparison of gastric luminal and gastric wall P_{CO_2} during hemorrhagic shock. *Circ Shock* 1993; **40**. 194–9

104 Nordin A, Makisalo H, Mildh L, Hockerstedt K Gut intramucosal pH as an early indicator of effectiveness of therapy for hemorrhagic shock *Crit Care Med* 1998; **26**: 1110–17

105 Odes HS, Hogan DL, Steinbach JH, Ballesteros MA, Koss MA, Isenberg JI Measurement of gastric bicarbonate secretion in the human stomach. different methods produce discordant results *Scand J Gastroenterol* 1992; **27**: 829–36

106 Ohri SK, Becket J, Brannan J, Keogh BE, Taylor KM. Effects of cardiopulmonary bypass on gut blood flow, oxygen utilization, and intramucosal pH. *Ann Thorac Surg* 1994; **57**· 1193–9

107 Olson D, Pohlman A, Hall JB. Administration of low-dose dopamine to nonoliguric patients with sepsis syndrome does not raise intramucosal gastric pH nor improve creatinine clearance *Am J Respir Crit Care Med* 1996, **154**: 1664–70

108 Pargger H, Staender S, Studer W, *et al* Occlusive mesenteric ischemia and its effects on jejunal intramucosal pH, mesenteric oxygen consumption and oxygen tensions of the jejunum in anesthesized pigs. *Intensive Care Med* 1997; **23**. 91–9

109 Parviainen I, Rantala A, Ruokonen E, Tenhunen J, Takala J. Angiotensin converting enzyme inhibition has no effect on blood pressure and splanchnic perfusion after cardiac surgery *J Crit Care* 1998; **13**: 73–80

110 Parviainen I, Ruokonen E, Takala J Dobutamine-induced dissociation between changes in splanchnic blood flow and gastric intramucosal pH after cardiac surgery *Br J Anaesth* 1995; **74** 277–82

111 Parviainen I, Ruokonen E, Takala J. Sodium nitroprusside after cardiac surgery: systemic and splanchnic blood flow and oxygen transport *Acta Anaesthesiol Scand* 1996, **40** 606–11

112 Parviainen I, Vaisanen O, Ruokonen E, Takala J. Effect of nasogastric suction and ranitidine on the calculated gastric intramucosal pH. *Intensive Care Med* 1996; **22**. 319–23

113 Riddington D, Venkatesh B, Clutton-Brock T, Bion J, Venkatesh KB. Measuring carbon dioxide tension in saline and alternative solutions: quantification of bias and precision in two blood gas analyzers. *Crit Care Med* 1994; **22**· 96–100

114 Riddington DW, Venkatesh B, Boivin CM, *et al.* Intestinal permeability, gastric intramucosal pH, and systemic endotoxemia in patients undergoing cardiopulmonary bypass *JAMA* 1996; **275** 1007–12

115 Rozenfeld RA, Dishart MK, Tonnessen TI, Schlichtig R. Methods for detecting local intestinal ischemic anaerobic metabolic acidosis by $P\mathrm{co}_2$ *J Appl Physiol* 1996, **81**· 1834–42

116 Rune SJ. Acid–base parameters of duodenal contents in man *Gastroenterology* 1972; **62**. 533–9

117 Salzman AL, Strong KE, Wang H, Wollert PS, Vandermeer TJ, Fink MP. Intraluminal 'balloonless' air tonometry a new method for determination of gastrointestinal mucosal carbon dioxide tension *Crit Care Med* 1994; **22**: 126–34

118 Sato Y, Weil MH, Tang W, *et al* Esophageal P_{CO_2} as a monitor of perfusion failure during hemorrhagic shock. *J Appl Physiol* 1997, **82** 558–62

119 Schlichtig R, Bowles SA Distinguishing between aerobic and anaerobic appearance of dissolved CO_2 in intestine during low flow. *J Appl Physiol* 1994, **76**· 2443–51

120 Schlichtig R, Mehta N, Gayowski TJ Tissue–arterial P_{CO_2} difference is a better marker of ischemia than intramural pH (pHi) or arterial pH–pHi difference *J Crit Care* 1996; **11**· 51–6

121 Smithies M, Yee TH, Jackson L, Beale R, Bihari D Protecting the gut and the liver in the critically ill: effects of dopexamine. *Crit Care Med* 1994; **22**: 789–95

122 Soong CV, Halliday MI, Barclay GR, Hood JM, Rowlands BJ, Barros D'Sa AA Intramucosal acidosis and systemic host responses in abdominal aortic aneurysm surgery. *Crit Care Med* 1997; **25** 1472–9

123 Steverink P, Moens Y, Kolkman JJ, De Vries JW. Gastrointestinal mucosa ischemia and cytokine response after *Escherichia coli* lipopolysaccharide challenge in anesthetized horses *Shock* (in press)

124 Steverink PJ, Kolkman JJ, Groeneveld AB, De Vries JW Catheter deadspace: a source of error during tonometry. *Br J Anaesth* 1998; **80**: 337–41

125 Tang W, Weil MHSS, Noc M, Gazmur RJ, Bisera J. Gastric intramural pCO_2 as monitor of perfusion failure during hemorrhagic and anaphylactic shock. *J Appl Physiol* 1994; **76**: 572–7

126 Taylor DE, Gutierrez G, Clark C, Hainley S. Measurement of gastric mucosal carbon dioxide tension by saline and air tonometry. *J Crit Care* 1997; **12**. 208–13

127 Temmesfeld-Wollbruck B, Szalay A, Mayer K, Olschewski H, Seeger W, Grimminger F. Abnormalities of gastric mucosal oxygenation in septic shock: partial responsiveness to dopexamine. *Am J Respir Crit Care Med* 1998; **157**. 1586–92

128 Temmesfeld-Wollbruck B, Szalay A, Olschewski H, Grimminger F, Seeger W. Advantage of buffered solutions or automated capnometry in air-filled balloons for use in gastric tonometry. *Intensive Care Med* 1997; **23**: 423–7

129 Uusaro A, Ruokonen E, Takala J. Splanchnic oxygen transport after cardiac surgery: evidence for inadequate tissue perfusion after stabilization of hemodynamics. *Intensive Care Med* 1996; **22**: 26–33

130 Vahl AC, Ozkaynak-Yilmaz EN, Nauta SH, *et al.* Endoluminal pulse oximetry combined with tonometry to monitor the perfusion of the sigmoid during and after resection of abdominal aortic aneurysm. *Cardiovasc Surg* 1997; **5**: 65–70

131 VanderMeer TJ, Wang H, Fink MP. Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Crit Care Med* 1995, **23**: 1217–26

132 Vervloet MG, Groeneveld ABJ, Kolkman JJ, Zwaarekant LJ. The role of antacids in gastrotonometry: an *in vitro* study. *Clin Intensive Care* 1998; **9**: 191–4

133 Von Montigny S, Laterre PF, Vanderelst P, De Kock M. The effects of intraoperative intravenous clonidine on gastric intramucosal P_{CO_2}. *Anesth Analg* 1998; **87**: 686–90

134 Walley KR, Friesen BP, Humer MF, Phang PT. Small bowel tonometry is more accurate than gastric tonometry in detecting gut ischemia. *J Appl Physiol* 1998; **85**: 1770–7

135 Welte M, Pichler B, Groh J, *et al.* Perioperative mucosal pH and splanchnic endotoxin concentration in orthotopic liver transplantation. *Br J Anaesth* 1996; **76**: 90–8

British Journal of Anaesthesia 84 (1): 87–8 (2000)

BJA

SHORT COMMUNICATIONS

Wound infiltration with bupivacaine after surgery to the cervical spine using a posterior approach

L. H. Pobereskin[1] and J. R. Sneyd[2]*

[1]Department of Neurosurgery and [2]Department of Anaesthesia, Derriford Hospital, Plymouth PL6 8DH, UK

**Corresponding author*

We have compared pain scores, morphine consumption and duration of stay for 50 adults who underwent elective cervical spine surgery via a posterior incision in a prospective, double-blind, placebo-controlled, randomized study. During wound closure, the paravertebral muscles and subcutaneous tissues were infiltrated with 40 ml of saline (control) or 0.25% bupivacaine. There were no significant differences in pain scores, morphine consumption or duration of stay between groups. In view of the potential risks of wound infiltration in the cervical region, we consider that this practice should be abandoned.

Br J Anaesth 2000; **84**: 87–8

Keywords: anaesthetics local, bupivacaine; anaesthetic techniques, regional, paravertebral; surgery spinal

Accepted for publication August 5, 1999

Wound infiltration with bupivacaine towards the end of surgery is commonly undertaken. However, evidence to support this practice in patients undergoing spinal surgery is inconclusive,[1–6] possibly because of variable methodology and, in some cases, inadequate blinding. The use of bupivacaine infiltration after surgery to the cervical spine has not been evaluated. We undertook a prospective, double-blind, placebo-controlled study to evaluate the effectiveness of paravertebral infiltration of bupivacaine after surgery to the cervical spine via a posterior approach.

Methods and results

All patients admitted to the Department of Neurosurgery at Derriford Hospital, Plymouth, UK in anticipation of operations for benign conditions of the cervical spine were approached to participate in this trial. Prior approval was obtained from the South and West Devon Health Authority Ethics Committee and patients gave written consent. Patients who were under 18 yr old, pregnant, or in whom it was expected that the dura would be opened were excluded.

Patients were premedicated with temazepam 10–20 mg and anaesthetized with propofol and fentanyl 2 $\mu g\ kg^{-1}$ followed by 0.5–1.5% isoflurane (end-tidal concentration) and 66% nitrous oxide in oxygen administered by mechanical ventilation. Additional fentanyl was given as indicated clinically. Neuromuscular block was achieved with vecuronium or atracurium and antagonized at the end of surgery using glycopyrrolate and neostigmine. Droperidol 0.5 mg was given as a prophylactic antiemetic

Before surgical incision, the skin and subcutaneous tissues were infiltrated with 20 ml of 1% lidocaine with epinephrine 1/200 000 to produce local vasoconstriction and minimize blood loss. Treatment allocation was determined by a computer-generated randomization scheme held in individually numbered sealed opaque envelopes After the surgical procedure had been completed and wound closure commenced, the anaesthetist opened the envelope and prepared the study solution (40 ml of 0.9% saline or 0.25% bupivacaine) in the anaesthetic room out of sight of the surgical team. The study solution was transferred to a sterile dish in the operative field from which it was drawn up into a sterile syringe for infiltration into the skin and paravertebral muscles under direct vision. This procedure ensured that all surgical staff were blinded to the study drug. No additional fentanyl was administered after infiltration of the study solution and the anaesthetist did not participate in collection of pain scores or decisions about times of patient discharge from hospital. All care after anaesthesia was given by nurses blinded to the treatment allocated.

In the postoperative recovery area, patients received morphine 2 mg i.v. at 5-min intervals until comfortable and subsequently used a patient-controlled analgesia (PCA) system programmed to give bolus doses of morphine 1 mg and droperidol 50 μg with a 5-min lockout and no background infusion.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Preoperative variables including age, sex, weight, duration of symptoms and operative indication were recorded. A baseline pain score was obtained from the patient using a 10-cm visual analogue scale (VAS) ranging from 'no pain' to the 'worst pain I can imagine'. It was emphasized that we were collecting data on spinal pain only, not radicular symptoms. Operative variables recorded included the number of levels operated on, length of incision, duration of operation, grade of operating surgeon, whether the operation was unilateral or bilateral and dose of fentanyl. VAS pain scores were recorded at 3, 12 and 24 h by nurses blinded to the study drug. Twenty-four hour morphine use was recorded.

Categorical variables were analysed using the chi-square test. Continuous variables were compared with the two independent samples *t* test or the Mann–Whitney *U* test where appropriate. The null hypothesis was rejected when $P<0.05$. The study number was decoded only after all patients had completed the study. Sample size was determined by an *a priori* power calculation based on our earlier study of patients undergoing lumbar spine surgery.[3] We felt that the smallest clinically significant difference in VAS scores and morphine use over 24 h would be 20 mm and 15 mg, respectively. Two groups of 25 patients were sufficient to detect these differences with an alpha error of 0.05 and a power of 80%.

Patient characteristics, preoperative pain scores and operative variables did not differ between groups. Pain scores at 3, 12 and 24 h after surgery, 24-h morphine use and duration of stay are shown in Table 1. There were no significant differences between groups.

Comment

We were unable to demonstrate a clinically useful reduction in postoperative pain or requirement for analgesia after surgery to the cervical spine after paravertebral infiltration with 0.25% bupivacaine 40 ml. All patients underwent wound infiltration with 1% lidocaine at the beginning of surgery. The use of lidocaine in this way is common surgical practice and has been included in at least three of the six reports which have compared bupivacaine and placebo after procedures on the lumbar spine.[1–6] We sought to mirror clinical practice in the design of this investigation and therefore gave lidocaine to both groups. We considered that the duration of action of lidocaine would have only modestly overlapped that of bupivacaine. However, if lack of a demonstrable bupivacaine effect were a result of a persistent action of lidocaine infiltration, then the additional use of bupivacaine would be unjustifiable.

Table 1 VAS pain scores, morphine consumption and duration of stay in the saline and bupivacaine groups (mean (SD)) [a]*t* test, [b]Mann–Whitney *U* test

	Saline	Bupivacaine	*P*
VAS (3 h)	40.4 (27.1)	35.7 (27.6)	0.54[a]
VAS (12 h)	30.9 (21.9)	32.1 (22.4)	0.85[a]
VAS (24 h)	33.6 (21.8)	33.5 (28.0)	0.982[b]
Morphine use (mg) (24 h)	32.0 (15.7)	37.6 (23.9)	0.34[a]
Duration of stay (days)	2.2 (1.1)	2.3 (0.67)	0.34[b]

In view of the potential risks of wound infiltration at the end of surgery, especially in the cervical region where inadvertent intrathecal or epidural block could cause serious and possibly life threatening complications, we consider that this practice should be abandoned.

References

1 Mullen JB, Cook WAJ. Reduction of postoperative lumbar hemilaminectomy pain with Marcaine. Technical note. *J Neurosurg* 1979; **51**: 126–7

2 Milligan KR, Macafee AL, Fogarty DJ, Wallace RG, Ramsey P. Intraoperative bupivacaine diminishes pain after lumbar discectomy. A randomised double-blind study. *J Bone Joint Surg Br* 1993; **75**: 769–71

3 Chadduck JB, Sneyd JR, Pobereskin LH. The role of bupivacaine in early postoperative pain control after lumbar decompression. *J Neurosurg (Spine 1)* 1999; **90**: 67–72

4 Cherian MN, Mathews MP, Chandy MJ Local wound infiltration with bupivacaine in lumbar laminectomy. *Surg Neurol* 1997; **47**: 120–3

5 Glasser RS, Knego RS, Delashaw JB, Fessler RG. The perioperative use of corticosteroids and bupivacaine in the management of lumbar disc disease. *J Neurosurg* 1993; **78**: 383–7

6 Teddy PJ, Fabinyi GC, Kerr JH, Briggs M. Bupivacaine infiltration after lumbar laminectomy. Local infiltration in the control of early postoperative lumbar laminectomy pain. *Anaesthesia* 1981; **36**: 380–3

British Journal of Anaesthesia 84 (1). 89–91 (2000)

Comparison of 1% ropivacaine with 0.75% bupivacaine and 2% lidocaine for peribulbar anaesthesia

G. Nicholson*, B. Sutton and G. M. Hall

Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK

**Corresponding author*

We have compared the efficacy of 1% ropivacaine with a mixture of 0.75% bupivacaine and 2% lidocaine for peribulbar anaesthesia in cataract surgery. We used the time to adequate block for surgery, and ocular and eyelid movement scores at 8 min after block as clinical end-points. Ninety patients were allocated randomly to receive 7–10 ml of a mixture of equal parts of 0.75% bupivacaine and 2% lidocaine or an equal volume of 1% ropivacaine alone. Hyaluronidase 15 iu ml^{-1} was added to both solutions. There were no differences between groups in clinical end-points. Median time at which the block was adequate to start surgery was 8 min (interquartile range 4–10 min) in each group. Median eyelid movement scores were similar in both groups, but the bupivacaine and lidocaine mixture produced a significantly decreased ocular movement score at 2, 4 and 6 min ($P<0.05$). There was no difference between groups in the incidence of minor complications. Based on clinical end-points, time to adequate block for surgery and median ocular and eyelid movement scores at 8 min, 1% ropivacaine as the sole agent for peribulbar anaesthesia was comparable with a mixture of 0.75% bupivacaine and 2% lidocaine.

Br J Anaesth 2000; **84**: 89–91

Keywords: anaesthetics local, ropivacaine; anaesthetics local, bupivacaine; anaesthetics local, lidocaine; anaesthetic techniques, regional, peribulbar

Accepted for publication. August 31, 1999

Regional anaesthesia with peribulbar block is the technique of choice for most patients undergoing cataract surgery.[1] A mixture of bupivacaine and lidocaine is the most frequently used local anaesthetic, lidocaine providing a rapid onset and bupivacaine a long duration of action.[2]

Ropivacaine is a new aminoamide local anaesthetic agent with a greater margin of safety than bupivacaine for cardiotoxicity and central nervous system toxicity.[3 4] We have shown recently that 1% ropivacaine is an effective alternative to 0.75% bupivacaine when used with 2% lidocaine for peribulbar anaesthesia.[5] We found that, although ocular movement scores were not significantly different between groups at 2, 4, 6 and 8 min, eyelid movement scores were significantly less in the ropivacaine group at 2, 6 and 8 min ($P<0.05$). The earliest time at which the block was considered adequate to start surgery was 8 min for each group.

However, if ropivacaine is used as a single agent for peribulbar anaesthesia, onset of block may be delayed. In this study, we have compared the rapidity of onset and efficacy of peribulbar block produced with 1% ropivacaine alone with the traditional mixture of equal volumes of 0.75% bupivacaine and 2% lidocaine; hyaluronidase was added to both solutions. The major clinical end-points were ocular and eyelid movement scores at 8 min, and time to adequate block for surgery.

Methods and results

After obtaining approval from the Local Research Ethics Committee and written informed consent, we studied 90 patients presenting for cataract surgery under local anaesthesia. This study had a 95% chance of detecting a statistically significant ($P<0.05$) difference of two points for the sums of the ocular movement scores. Patients were excluded if they were unwilling to take part, if there were communication problems or if there was a history of allergy to amide-type local anaesthetic agents. Patients were allocated randomly to one of two groups using sealed envelopes. Sealed unmarked envelopes that contained the name of the anaesthetic to be administered were randomized by shuffling One group received a mixture of equal volumes of 2% lidocaine and 0.75% bupivacaine, with hyaluronidase 15 iu ml^{-1}, while the other group received an equivalent volume of 1% ropivacaine to which hyaluronidase 15 iu ml^{-1} was added. The anaesthetic solution was warmed to

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

body temperature using a fibrinotherm (Ernst Biegler Ges. mbh, Austria).

Patients were not fasted and did not receive any premedication, perioperative sedation or supplementary oxygen. On arrival in the induction room, baseline eyelid and globe movements were assessed. Topical anaesthesia of the conjunctiva and cornea was achieved by administering 2–3 drops of 0.4% oxybuprocaine. Standard monitoring was started and i.v. access established. Peribulbar block was carried out by one of two consultant anaesthetists via a single inferolateral, transcutaneous or transconjunctival injection using a 25-gauge, 25-mm needle. After test aspiration, 7–10 ml of the local anaesthetic mixture was injected over 30–40 s. Different volumes of local anaesthetic were used depending on the degree of filling of the orbit observed during injection and the rate of onset of ptosis. Manual compression and gentle massage of the eyeball were performed after which a Visitec intraocular pressure reducer inflated to 40 mm Hg was applied between scoring to facilitate spread of the anaesthetic solution and to lower intraocular pressure. Patients were assessed for eyelid and ocular movements at 2-min intervals using the scoring system of Brahma and colleagues.[6] Scoring was carried out by a trained observer who was blinded to the local anaesthetic used.

Ocular movements were scored for each direction of gaze in the superior, inferior, medial and lateral directions with a maximum score for each direction of three points and a possible total maximum score of 12 points. Ocular and eyelid movements were assessed at 2, 4, 6, 8 and 10 min until the block was considered adequate for surgery (eyelid movement score=0 and ocular movement score ≤2). If after 10 min block was inadequate, supplementary anaesthesia was provided with another injection of up to 5 ml of the test solution using the same technique. Time to adequate surgical anaesthesia was noted in addition to the need for supplementary anaesthesia. It was assumed that, when motor block had been achieved, adequate sensory block was already present as this usually precedes motor block. Complications during or after injection were recorded and patients were questioned specifically about pain during insertion of the block or during surgery.

The main outcome criteria were difference in median ocular and eyelid movement scores at 8 min and time needed to obtain adequate block to start surgery. Differences between .groups were analysed using the Wilcoxon rank sum test. The number of patients who reached an ocular movement score of ≤1, need for further injections, delay to the start of surgery and occurrence of complications were compared, using the chi-square or Fisher's exact test, as appropriate. Statistical analysis was carried out using SPSS for Windows version 8.

There were 45 patients in each group and all patient data were included in the statistical analysis. Mean age in the bupivacaine group was 75 (range 51–92) yr and 73 (41–98) yr in the ropivacaine group. The male:female ratio was 19:26 in the bupivacaine group and 15:30 in the ropivacaine group.

Table 1 Median (interquartile range) ocular and eyelid movement scores and number of patients who required supplementary anaesthesia or developed complications in the two groups. *$P<0.05$ between groups

	Bupivacaine 0.75% and 2% lidocaine ($n = 45$)	**Ropivacaine 1% ($n = 45$)**
Ocular movement scores		
2 min	5 [3–7]*	7 [5–8]
4 min	3 [2–6]*	5 [3–7]
6 min	2 [1–5]*	4 [2–6]
8 min	2 [0–4]	2 [1–5]
Eyelid movement scores		
2 min	1 [1–2]	1 [1–2]
4 min	1 [0–2]	1 [0–2]
6 min	0 [0–2]	1 [0–2]
8 min	0 [0–1]	0 [0–1]
Supplementary anaesthesia	9	14
Complications		
Haematoma	–	1
Chemosis	7	6
Pain	11	13

Median eyelid movement scores were not significantly different between groups at any time. Ocular movement scores were significantly decreased in the bupivacaine group compared with the ropivacaine group at 2 min (P=0.011), 4 min (P=0.022) and 6 min (P=0.047), but there was no significant difference between groups at 8 min (P=0.13) (Table 1). Median time at which the block was considered adequate to start surgery was 8 min (interquartile range 4–10 min) for each group.

Twenty patients in the bupivacaine group and 13 in the ropivacaine group had ocular movement scores ≤1 at 8 min. One patient in each group had an ocular movement score of 12 at 8 min (total failure of the block). Fourteen patients in the ropivacaine group and nine in the bupivacaine group required supplementary analgesia, but surgery was delayed in only one patient in each group. Minor complications occurred in seven patients in each group: seven patients in the bupivacaine group and six in the ropivacaine group had subconjunctival chemosis and one patient in the ropivacaine group developed a periorbital haematoma, which was small. All cases of chemosis had resolved by the start of surgery. Thirteen patients in the ropivacaine group complained of slight pain during insertion of the initial block compared with 11 patients in the bupivacaine group. None of the differences was statistically significant.

Comment

We have shown that 1% ropivacaine alone is an effective alternative to 0.75% bupivacaine and 2% lidocaine for peribulbar anaesthesia. Although the bupivacaine and lidocaine mixture resulted in significantly lower ocular movement scores at 2, 4 and 6 min, at 8 min both anaesthetic solutions provided similar anaesthesia. The faster onset in the bupivacaine and lidocaine group was probably the effect of lidocaine.

We were unable to assess the duration of motor block as patients' eyes were bandaged and covered after operation and they were discharged home 1–2 h after surgery. If a shorter duration of motor block occurs with ropivacaine, this could be advantageous as prolonged paralysis from local anaesthesia leaves the eye vulnerable to drying and trauma.[7]

Peribulbar anaesthesia requires relatively large volumes of local anaesthetic and concerns have been expressed about the potential for systemic toxicity. The incidence of peribulbar blocks requiring supplementary anaesthesia has been reported to be as high as 54%.[8] Huha and colleagues recently compared the clinical efficacy of 1% ropivacaine alone with 0.75% bupivacaine and found no difference in perioperative analgesia or duration of akinesia.[9] Those patients who received 1% ropivacaine had higher maximum serum concentrations of local anaesthetic compared with the group who received 0.75% bupivacaine. However, no drug-related adverse effects were observed in either group. Ropivacaine is less toxic to the myocardium and central nervous system, which is a theoretical advantage in elderly patients who frequently have co-existing cardiac disease.

Acknowledgement

We gratefully acknowledge the support of Astra Pharmaceuticals who provided supplies of ropivacaine.

References

1. Barker JP, Vafidis GC, Hall GM. Postoperative morbidity following cataract surgery. A comparison of local and general anaesthesia *Anaesthesia* 1996; **51**: 435–7
2. Wong DHW. Regional anaesthesia for intraocular surgery. *Can J Anaesth* 1993; **40**: 635–57
3. McClure JH. Ropivacaine *Br J Anaesth* 1996; **76**. 300–7
4. Knudsen K, Beckman M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14
5. Nicholson G, Sutton B, Hall GM. Ropivacaine for peribulbar anesthesia. *Reg Anesth* 1999; **24**: 337–40
6. Brahma AK, Pemberton CJ, Ayeko M, Morgan LH. Single medial injection peribulbar anaesthesia using prilocaine. *Anaesthesia* 1994; **49**. 1003–5
7. Johnson RW. Anatomy for ophthalmic anaesthesia. *Br J Anaesth* 1995; **75**: 80–7
8. Loots JH, Koorts AS, Venter JA. Peribulbar anesthesia. A prospective statistical analysis of the efficacy and predictability of bupivacaine and a lidocaine/bupivacaine mixture *J Cataract Refract Surg* 1993; **19**: 72–6
9. Huha T, Ala-Kokko I, Salomaki T, Alahuhta S. Clinical efficacy and pharmacokinetics of 1% ropivacaine and 0 75% bupivacaine in peribulbar anaesthesia for cataract surgery. *Anaesthesia* 1998; **54**. 137–41

British Journal of Anaesthesia 84 (1): 92–4 (2000)

Effects of respiratory and metabolic pH changes and hypoxia on ropivacaine-induced cardiotoxicity in dogs

J. M. Porter[1]*, F. Markos[2], H. M. Snow[2] and G. D. Shorten[1]

[1]*Department of Anaesthesia and Intensive Care Medicine and* [2]*Department of Physiology,*
University College Cork, Cork, Republic of Ireland

**Corresponding author*

We have studied the effects of acute changes in acid–base status and hypoxia on the cardiotoxic effects of intracoronary injection of ropivacaine in anaesthetized dogs. The effects of intracoronary ropivacaine were compared when ropivacaine was administered during eucapnia and during each of another nine states in random order: hypocapnia, hypercapnia, hypoxia, metabolic alkalosis, metabolic acidosis, combined metabolic acidosis and hypocapnia, combined metabolic alkalosis and hypercapnia, combined hypoxia and hypercapnia, and combined metabolic acidosis and hypoxia. Hypocapnic alkalosis consistently reduced the cardiotoxic effects of intracoronary ropivacaine ($P<0.01$). Our findings indicate that induction of hypocapnic alkalosis may provide a useful adjunct to standard resuscitative measures after inadvertent administration of amide local anaesthetic agents.

Br J Anaesth 2000; **84**: 92–4

Keywords: anaesthetics local, ropivacaine; toxicity, ropivacaine; heart, myocardium; dog

Accepted for publication: June 30, 1999

Cardiovascular collapse can occur after inadvertent intravascular injection of bupivacaine. Bupivacaine causes arrhythmias by producing a unidirectional conduction block which facilitates re-entry.[1] Ropivacaine is an amide local anaesthetic, structurally similar to bupivacaine, but prepared as a pure S-enantiomer. The cardiodepressant and electrophysiological toxicity ratios for bupivacaine to ropivacaine are 4:3 and 15:6.7, respectively.[2]

Severe hypoxia, hypercapnia and acidosis can develop rapidly after local anaesthetic-induced seizures. Acidosis and hypoxia have been demonstrated to enhance the negative inotropic and chronotropic effects of bupivacaine.[3] In this study, we have examined the effects of respiratory and metabolic changes in pH and hypoxia on ropivacaine-induced cardiotoxicity in dogs.

Methods and results

The study was carried out by licensed investigators in compliance with the Cruelty to Animals Act 1876 (Department of Health, Ireland). Labrador dogs (mean weight 21.1 (range 19–24.5) kg) were premedicated with morphine 10 mg s.c. and anaesthetized with pentobarbital i.v. (induction 30 mg kg^{-1}, maintenance 3 mg kg^{-1} every 30 min). After tracheostomy, thoracotomy was performed through the sixth left intercostal space and a 5-F catheter-tipped manometer was inserted into the cavity of the left ventricle. Cardiac output was measured using a transit time perivascular flowprobe (Transonic flowmeter, Linton Instruments) placed around the ascending aorta. A 24-gauge catheter was introduced into the left circumflex coronary artery under direct vision.

The dose of ropivacaine which produced a reduction in d*P*/d*t* of approximately 25% was ascertained in each animal. A placebo (normal saline 2 ml) was injected before administration of ropivacaine into the circumflex artery. The effects of intracoronary ropivacaine were assessed during eucapnia (Pa_{CO_2} 5.3–6.0 kPa) and during each of another nine states induced in random order. These were: hypocapnia (Pa_{CO_2} 3.3–4.0 kPa); hypercapnia (Pa_{CO_2} 7.3–8.0 kPa); hypoxia (Pa_{O_2} <5.3 kPa); metabolic alkalosis (pH 7.48–7.54); metabolic acidosis (pH 7.22–7.29); combined metabolic acidosis and hypocapnia (non-respiratory pH 7.2, Pa_{CO_2} 3.3–4.0 kPa); combined metabolic alkalosis and hypercapnia (non-respiratory pH 7.5, Pa_{CO_2} 7.3–8.0 kPa); combined hypoxia and hypercapnia; and combined metabolic acidosis and hypoxia (as defined previously).

When the animal had recovered from the effects of the drug, ventilation was adjusted or either hydrochloric acid or sodium bicarbonate infusions commenced to induce the next study state. The changes produced by intracoronary ropivacaine for the measured variables were compared during eucapnia with those which occurred in each of the induced states, and the data were analysed using the Student's paired *t* test (Bonferroni correction for nine within-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Changes in haemodynamic and electrocardiographic (V5) variables after intracoronary injection of ropivacaine 0.5–8 mg under different acid–base conditions in anaesthetized dogs. **P=0.01 compared with during eucapnia †A negative value in this row indicates a reduction in the absolute value of negative d*P*/d*t* MAP=Mean arterial pressure, CO=cardiac output, d*P*/d*t*=first derivative of LVP (positive=systole, negative=diastole), met =metabolic. Data are mean (SD)

	Eucapnia (*n* = 8)	**Hypocapnia** (*n* = 12)	**Hypercapnia** (*n* = 7)	**Hypoxia** (*n* = 6)	**Met. alkalosis** (*n* = 6)	**Met. acidosis** (*n* = 6)	**Hypercapnic alkalosis** (*n* = 5)	**Hypocapnic acidosis** (*n* = 5)	**Hypercapnic hypoxia** (*n* = 4)	**Hypoxic acidosis** (*n* = 5)
MAP (%)	–3.0 (5.4)	–1.6 (4.4)	–24.1 (34.1)	–3.8 (5.4)	3.0 (5.6)	–4.3 (5.6)	–1.2 (3.3)	3.1 (5.0)	–13.9 (21.0)	0.9 (4.0)
CO (%)	–5.9 (10.0)	–1.5 (16.4)	–15.3 (12.6)	–5.7 (11.4)	–7.4 (8.1)	–6.3 (4.9)	–7.0 (7.5)	–8.4 (7.8)	–10.1 (24.1)	–1.1 (3.5)
d*P*/d*t* (%)	–22.8 (5.6)	–11.2 (2.7)**	–0.25 (0.01)	–16.2 (17.9)	–17.6 (19.0)	–16.1 (9.0)	–6.3 (19.6)	–27.5 (12.0)	–1.6 (44.2)	–22.1 (18.8)
Negative d*P*/d*t* (%)†	–20.3 (18.0)	10.8 (13.5)	–13.6 (27.9)	–12.3 (20.9)	–4.4 (17.7)	–4.4 (22.1)	–3.1 (21.7)	–15.9 (23.0)	–31.9 (62.2)	11.7 (21.9)
ST (mV)	0.37 (0.2)	0**	0.2 (1.7)	0.1 (0.1)	0.01 (0.01)	0.2 (0.2)	0.2 (0.3)	0.3 (0.3)	0.2 (0.19)	0.3 (0.26)

subject comparisons). $P<0.01$ was considered statistically significant.

We studied 13 Labrador dogs. Initially, eight dogs were studied, of which three died before completion of all 10 states (ventricular fibrillation (VF): one each following intracoronary ropivacaine during eucapnia, metabolic acidosis and metabolic acidosis–hypoxia). Findings from these eight dogs indicated a potential protective effect of hypocapnia and therefore another five dogs were studied in this state.

The doses of ropivacaine administered (based on the initial dose-finding study) were 0.5–8 mg. Haemodynamic variables and ST changes after intracoronary ropivacaine in each of the 10 states are summarized in Table 1.

Induced hypocapnia (respiratory alkalosis) was associated with a significant reduction in the magnitude of ropivacaine-induced ST depression in the V5 lead (0 mV during hypocapnia, 0.4 (0.2) mV during eucapnia; P=0.002). Hypocapnia was also associated with a reduction (which did not reach statistical significance, as defined previously) in the magnitude of the effect of ropivacaine on LV d*P*/d*t*max (11.2 (2.7)% during hypocapnia compared with 22.8 (5.6)% during eucapnia; P=0.01). The fatal dose of ropivacaine, determined for each animal, produced progressive widening of the QRS complex followed by coarse ventricular fibrillation.

Comment

The most important finding of our study was that induced hypocapnia before administration of intracoronary ropivacaine to anaesthetized dogs decreased the magnitude of cardiotoxic effects (ST segment and to a lesser extent left ventricular d*P*/d*t* changes). Initially, eight dogs were studied. Of these, hypocapnia was studied in seven (one dog died before induction of the hypocapnic state). As a potentially beneficial effect of hypocapnia was demonstrated, we decided to study another five dogs in which hypocapnia was induced; therefore, a total of 12 dogs were studied in the hypocapnic state.

The intracoronary route was selected to allow induction of reproducible cardiotoxic effects after ropivacaine doses of 0.5–8 mg, which were small and therefore unlikely to produce systemic effects or accumulate. A second deficiency of the model was that only the lateral wall of the left ventricle was exposed to ropivacaine. Third, pentobarbital, a potent anticonvulsant, was selected as the anaesthetic agent to examine cardiotoxicity in the absence of confounding central nervous system effects. Fourth, changes in acid–base status were induced before administration of ropivacaine, thereby limiting extrapolation to the clinical setting.

Each dog served as its own control with respect to both the individual dose chosen and the cardiotoxic changes observed during eucapnia.

Individual anatomical variation in the relationship of the great coronary vein to the circumflex artery determined the site at which the artery was cannulated: this accounted for the variety of cannula positions and consequently the different doses (0.5–8 mg) administered. ST segment depression associated with administration of an amide local anaesthetic agent has not been documented previously in the absence of significant QRS widening.[2] The mechanism of this ropivacaine-induced ST segment change is unclear. it is unlikely to reflect myocardial ischaemia as it consistently occurred within 5 s of drug administration.

Differential tissue uptake of amide local anaesthetics appears to correlate with lipid solubility.[4] However, in a study of myocardial uptake of local anaesthetics in sheep, a similar percentage of the injected dose of lidocaine, bupivacaine and ropivacaine was found in the myocardium, despite differences in lipid solubility.[5] This suggests that intrinsic pharmacological differences appear to be important with respect to cardiotoxicity rather than selective uptake into the myocardium.

The results of our study suggest that induction of hypocapnic alkalosis may provide a useful adjunct to standard resuscitative therapy after intravascular administration of amide local anaesthetic agents.

Acknowledgements

We are grateful to Kathleen O'Sullivan, MSc, Department of Statistics, University College Cork, for statistical advice and to Kieran O'Donnell and Stephen Dineen, Department of Physiology, University College Cork, for technical assistance

References

1 Calvey TN, Williams NE Local anaesthetic agents. In. Calvey TN, Williams NE eds. *Principles and Practice of Pharmacology for*

Anaesthetists. Oxford. Blackwell Scientific, 1991; 228–55

2 Reiz S, Haggmark G, Nath S. Cardiotoxicity of ropivacaine—a new amide local anaesthetic agent. *Acta Anaesthesiol Scand* 1989; **33**: 93–8

3 Sage DJ, Feldman HS, Arthur R, et *al.* Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. *Anesth Analg* 1984; **63**: 1–7

4 Halpern SH, Eisler EA, Shnider SM, *et al.* Myocardial tissue uptake of bupivacaine and lidocaine after intravenous injection in normal and acidotic rabbits. *Anesthesiology* 1984; **A208**: 61

5 Gherardini G, Samuelson U, Jernbeck J, Aberg B, Sjostrand N. Comparison of vascular effects of ropivacaine and lidocaine on isolated rings of human arteries. *Acta Anaesthesiol Scand* 1995; **39**: 765–8

British Journal of Anaesthesia **84** (1) 95–6 (2000)

I.v. regional diamorphine for analgesia after foot surgery

M. G. Serpell[1]*, E. Anderson[2], D. Wilson[2] and N. Dawson[2]

[1]Department of Anaesthesia and [2]Department of Orthopaedic Surgery,
Western Infirmary, Glasgow G11 6NT, UK

**Corresponding author*

Opioids administered to peripheral tissues can have significant analgesic effects in doses which would not be effective centrally. We have assessed the effects of regional diamorphine 2.5 mg i.v. in 14 patients undergoing surgical correction of bilateral arthritic foot deformities in a prospective, randomized, double-blind study. Patients acted as their own controls as only one foot received the active drug. Visual analogue scale (VAS) pain scores and wound tenderness were measured over 72 h. Diamorphine did not improve median VAS area under the curve pain scores during the first 6 h after surgery (33 (95% confidence intervals (CI) 25–46) *vs* 24 (17–35)). It also did not effect wound hypersensitivity when tested at 72 h after surgery (95 (47–125) *vs* 90 (50–125) g). There were no significant adverse effects.

Br J Anaesth 2000; **84**: 95–6

Keywords: analgesics opioid, diamorphine; anaesthetic techniques, regional, i.v.; surgery, orthopaedic

Accepted for publication: July 16, 1999

When opioids are applied peripherally to tissues, they can have significant analgesic effects in doses which would not be effective centrally.[1] This action may be explained by activation of opioid receptors at peripheral sites located in inflamed tissue. Our previous study failed to show any improvement in analgesia or hyperalgesia after peripheral administration of morphine for bilateral foot surgery.[2] We postulated that this may have been because of poor access of morphine to the receptors in the tissues of the foot. Therefore, we have repeated this prospective, randomized, double-blind, placebo-controlled study with a more lipophilic opioid and a larger volume of injectate.

Methods and results

After obtaining approval from the Hospital Ethics Committee and written informed consent, we studied 14 patients undergoing elective surgery for correction of bilateral arthritic deformities of the feet. Patients were ASA I–II, aged 18–80 yr and weighed 45–90 kg. All anti-inflamatory medication was stopped 72 h before surgery; paracetamol was taken if required for analgesia.

Anaesthesia was induced with propofol and maintained with 1–2% enflurane and 66% nitrous oxide in oxygen, with the patient breathing spontaneously via a laryngeal mask. Each foot was cannulated with a 22-gauge i.v. Venflon and exsanguinated using an Esmarch bandage. Tourniquets were applied just above the ankle and inflated to 100 mm Hg above systolic arterial pressure. Patients received 15 ml of 0.9% saline containing diamorphine 2.5 mg into the cannula of one foot and 15 ml of saline into the other over 60 s. This procedure was randomized (Kwickstat 3.01 TexaSoft) and double-blinded. The cannulae were removed and surgery commenced 10 min later on each foot by two operators simultaneously using the same technique Morphine was administered systemically after commencement of surgery, as required, by i.v. injection. After surgery, the tourniquets were deflated and analgesia was provided in the recovery room by bolus doses of morphine 1–2 mg i.v., as requested, until satisfactory relief was obtained.

After 2 h, patients returned to the ward and analgesia was provided by paracetamol 1 g, ibuprofen 400 mg or morphine 7.5–10 mg i.m. Pain scores were measured separately for each foot at 1, 2, 4, 6, 24, 48 and 72 h using a 100-mm visual analogue scores (VAS). At 72 h, sensitivity thresholds were assessed by applying wires to the dominant forearm and to both feet on an area 2 cm lateral to the proximal end of the wound The six calibrated wires of increasing gauge allowed application of a range of forces to the skin (5, 10, 40, 50, 135 and 230 g). The force values were recorded when touch was first detected and when the stimulus first became uncomfortable, and are expressed as relative thresholds (forearm minus foot) so that each patient acted as their own control.

Power analysis indicated that 12 patients would be needed to detect a 50% difference in pain levels with a power of 80% and significance of 0.05 (from area under the curve (AUC) data–SD of 42%).[3 4] Data were analysed using Mintab 10.5 for Windows 95.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

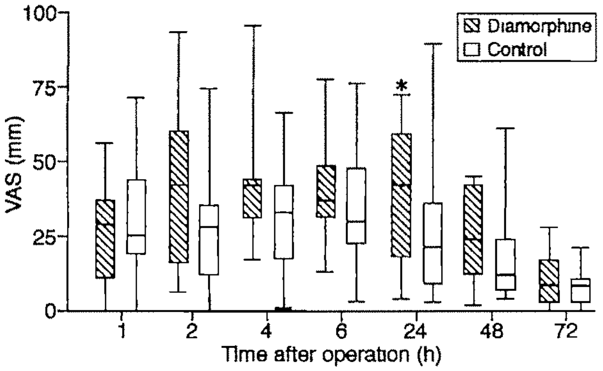


Fig 1 Median, interquartile and full range of visual analogue scale (VAS) pain scores for the diamorphine and control groups at various individual postoperative times. *P=0.05 (Wilcoxon sign rank test).

One patient was withdrawn from the study because the injectate leaked from the Venflon. There were no differences between groups in operator seniority or tourniquet time. Relative median pain thresholds were 95 (95% confidence intervals (CI) 47–125) g and 90 (50–125) g for the diamorphine and control groups, respectively. Mean doses of systemic morphine given during and after operation were 6.5 (SD 3) and 9.3 (7.9) mg, respectively.

VAS values at individual times are presented in Figure 1. Median (interquartile) scores tended to be higher in the diamorphine group but this only just reached significance at 24 h (42 (18–59) *vs* 21 (9–36), respectively; P=0.05 Wilcoxon sign rank test). AUC pain scores for the first 6 h were not significantly different (median 33 (95% CI 25–46) for diamorphine and 24 (17–35) for controls).

The only adverse effect noted was flushing of the foot which occurred in one patient in each group.

Comment

Diamorphine did not appear to have an effect on postoperative pain or secondary hyperalgesia. Diamorphine may have failed to gain access to the peripheral receptors. Some leakage of drug into the general circulation can occur through both intraosseous and other veins, but we took steps to prevent this by ensuring that the tourniquet completely encircled the lower calf, that exsanguination was performed and the injection was given slowly. We did not observe any seepage of the injectate from the wound during surgery.

Diamorphine is lipophilic and would be expected to have high tissue uptake and gain access to the peripheral receptors in the nerve and joint tissue.[5] However, when the tourniquet is deflated, the drug may be washed out rapidly and any peripheral effect of the opioid could then be obscured by the central effects which would produce analgesia of both feet. In support of this, during the pilot phase of the study, when diamorphine 5 mg was given, one patient required naloxone to reverse respiratory depression which occurred immediately after deflation of the tourniquet. These systemic effects did not occur with the dose of 2.5 mg.

Similarly, the dose of morphine given systemically and paracetamol and ibuprofen analgesic consumption would have had a central analgesic effect which would be equal for both feet and may have attenuated any potential differences. However, it would have been unethical to withhold these drugs as optimal analgesia must remain a priority for patients after surgery.

Analgesia has been reported with morphine 1 mg administered arthroscopically[1] but the area is relatively avascular and so the drug is likely to remain localized when the tourniquet is deflated. Consequently, application of opioids into the knee joint seems to be beneficial while other peripheral routes of administration do not.[6]

The main analgesic effect would be expected to occur in the early postoperative period and we doubt the clinical significance of the 24-h VAS recording. The lower pain thresholds in the feet are indicative of secondary hyperalgesia which can result from both peripheral and central sensitization. The fact that diamorphine was not effective despite being administered peripherally and *before* surgery was commenced, supports a larger role for central sensitization in this phenomenon.

We used a sensitive model for this investigation.[3] Patients were their own controls and therefore differences in the comprehension and reporting of pain, and the pharmacodynamic and kinetic profile of any drug, would not be responsible for differences seen in either foot.

In summary, i.v. regional diamorphine 2.5 mg had no beneficial effect on pain scores or wound hypersensitivity during the first 72 h after surgical correction of arthritic foot deformities.

References

1 Stein C, Comisel K, Haimerl E, *et al.* Analgesic effect of intraarticular morphine after arthroscopic knee surgery. *N Engl J Med* 1991; **325**: 1123–6
2 Serpell MG, Marshall S, Anderson E, Cullen T, Abernethy J. Intravenous regional morphine for analgesia after foot surgery. *Analgesia* 1995; **1**: 719–22
3 McQuay H, Weir L, Porter B, *et al.* A model for comparison of local anesthetics in man. *Anesth Analg* 1982; **61**: 418–22
4 du V Florey C. Sample size for beginners. *BMJ* 1993; **306**. 1181–4
5 Sawynok J. The therapeutic use of heroin: a review of the pharmacological literature. *Can J Physiol Pharmacol* 1986; **64**: 1–6
6 McQuay HJ, Moore RA. Pain relief with intra-articular morphine after knee surgery and analgesic efficacy of peripheral opioids. In: McQuay HJ, Moore RA, eds. *An Evidence-Based Resource for Pain Relief.* Oxford: Oxford University Press, 1988, 147–63

British Journal of Anaesthesia 84 (1): 97–9 (2000)

Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers

T. M. Buetler[1 5], O. H. G. Wilder-Smith[2], C. H. Wilder-Smith[1 2], S. Aebi[3], T. Cerny[4] and R. Brenneisen[1]*

[1]Department of Clinical Research, University of Bern, Murtenstrasse 35, CH-3010 Bern, Switzerland.
[2]Nociception Research Group, Bubenbergplatz 11, CH-3011 Bern, Switzerland.
[3]Institute for Medical Oncology, Inselspital, CH-3010 Bern, Switzerland.
[4]Kantonsspital St. Gallen, CH-9007 St. Gallen, Switzerland
[5]Present address: Pharmacology Group, School of Pharmacy, University of Lausanne, CH-3010 Bern, Switzerland
**Corresponding author*

The pharmacodynamics of morphine-6-glucuronide (M-6-G) i.v. were assessed in 12 healthy male volunteers in an open study. After a single bolus dose of M-6-G 5 mg i.v., we measured antinociceptive effects, using electrical and cold pain tests, and plasma concentrations of M-6-G, morphine-3-glucuronide (M-3-G) and morphine. Pain intensities during electrical stimulation (at 30, 60 and 90 min after injection) and ice water immersion (at 60 min) decreased significantly ($P<0.005$) compared with baseline. Mean plasma peak concentrations of M-6-G were 139.3 (SD 38.9) ng ml^{-1}, measured at 15 min. Our data demonstrate that M-6-G has significant analgesic activity.

Br J Anaesth 2000; **84**: 97–9

Keywords: analgesics opioid, morphine; analgesics opioid, morphine-6-glucuronide; pain, experimental; pharmacodynamics

Accepted for publication: July 26, 1999

The major metabolites of morphine are morphine-6-glucuronide (M-6-G) and morphine-3-glucuronide (M-3-G).[1] M-6-G has a 100-fold higher affinity for μ opioid receptors compared with morphine when given intrathecally, and shows analgesic activity.[2] Systemic M-6-G has been shown to be approximately equipotent to morphine with respect to analgesic activity but with fewer side effects.[2] However, a recent study failed to demonstrate analgesic activity of M-6-G i.v. in healthy volunteers.[3] In this study, we have examined the analgesic activity of M-6-G i.v. in human volunteers using opioid sensitive pain tests, and related this to plasma concentrations.

Methods and results

After obtaining approved from the Ethics Committee of the University of Berne and written informed consent, we studied 12 healthy male volunteers (aged 21–46 yr, weight 53–80 kg) in an open study. Before injection of M-6-G, a baseline blood sample was obtained from the right antecubital vein and control pain tests conducted. After a light standardized meal, M-6-G 5 mg (Lipomed, Allschwil, Switzerland; >98.5% HPLC purity), dissolved shortly before use in sterile isotonic saline 5 ml, was injected as an i.v. bolus dose over 1 min. Blood samples were obtained every 15 min for the first 2 h and then hourly until the end of the study (5 h). One subject received M-6-G 10 mg and another subject 20 mg orally.

Subjects were instructed in detail concerning the pain tests and a practice run was performed before actual data collection. During testing, subjects were in a quiet, warm room, in a comfortable sitting position. Two standardized tests were performed. In the ice bucket pain test, the non-dominant hand was immersed in an ice water bath maintained at a constant temperature of 4°C and pain intensity was noted after 170 s on a 100-mm visual analogue scale (VAS; 0=no pain, 100=unbearable pain). In the electrical pain stimulation test, the pain tolerance threshold was determined by increasing the current applied with an electrical nerve stimulator (100 Hz tetanic stimulation, Digistim, Biometer A/S, Copenhagen, Denmark) to the thenar eminence of the dominant hand by 0.1 mA s^{-1} until the pain sensation became 'intolerable'. Prior reduction of skin resistance was ensured by degreasing and scrubbing the skin with emery paper. The tolerance threshold current was applied on two occasions for 30 s and pain scores were noted on a VAS. Both pain tests were performed 10 min before and 30, 60, 90, 120, 180 and 300 min after injection of M-6-G. Side effects were noted.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

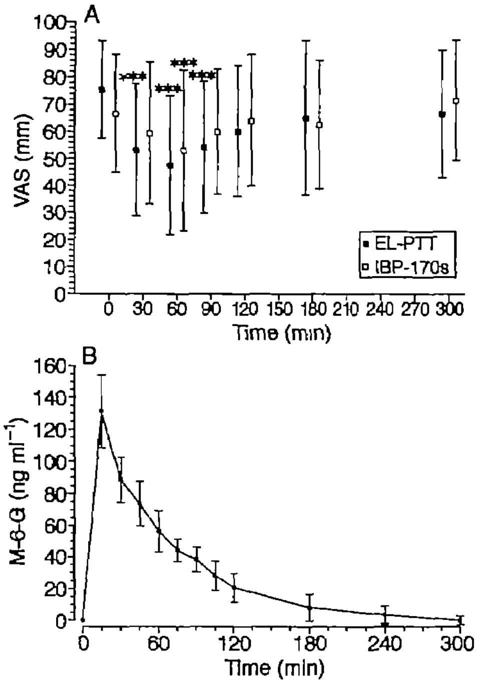


Fig 1 Antinociceptive effects and plasma concentrations of M-6-G A: Mean (SD) visual analogue pain scores (VAS) of pain intensity (0=no pain, 100=unbearable pain) during ice bucket immersion and electrical stimulation at 200% pain tolerance thresholds in 12 healthy volunteers EL-PTT=Electrical pain tolerance thresholds, IBP-170s=ice bucket pain test lasting 170 s ***$P<0.001$ *vs* pre-M-6-G baseline B. Mean (SD) plasma concentrations of morphine-6- glucuronide (M-6-G)

Statistical analysis was performed using analysis of variance (ANOVA) and *post hoc* Tukey's honest significance test. $P<0.05$ was considered significant.

Concentrations of M-6-G, M-3-G and morphine in plasma were assayed by high-pressure liquid chromatography with diode-array detection (HPLC-DAD).[4]

All 12 volunteers completed the pain tests. There were no serious or objective side effects. Subjective effects were sensations of heaviness, warmth and faster pulse (12 of 12 subjects), nervousness (seven), shortness of breath (three) and localized rash (three).

The time–effect for pain intensities during both the ice bucket and electrical pain tests was highly significant ($P<0.0001$) (Fig. 1A). Pain intensities during electrical stimulation were significantly lower than baseline at 30, 60 and 90 min after administration of M-6-G ($P<0.0005$). With the ice bucket test, pain intensity at 60 min was significantly lower than that at baseline ($P=0.004$). At other times differences were not significant. In two subjects who received oral M-6-G, no effects on nociception were observed.

M-6-G was present in plasma only after i.v. administration. Peak plasma concentrations of M-6-G of 90–228 ng ml^{-1} (mean 139.3 (SD 38.9) ng ml^{-1}) were measured at 15 min (Fig. 1B). Morphine was not detectable.

Comment

We have demonstrated that M-6-G has analgesic activity in human volunteers after i.v. application when appropriate and sensitive pain tests are used, corroborating earlier studies in patients and healthy subjects.[2] In contrast, a recent placebo- and morphine-controlled study[3] reported a lack of analgesic activity after constant infusion of M-6-G, although steady-state M-6-G plasma concentrations (70–175 ng ml^{-1}) were similar to those in our study (90–228 ng ml^{-1}). However, the study of Loetsch and colleagues[3] must be interpreted with caution because of the very high incidence of opioid effects and use of naloxone and antiemetics almost exclusively in the morphine group. The resultant unblinding may have prejudiced volunteer reactions and it is possible that the rescue medication itself had effects on nociception. Moreover, the pain-evoked cerebral late potentials used in their study are recognized to be multifactorial in origin and cannot be assumed to measure sensory discriminative responses to pain, but rather reflect emotional–motivational aspects of pain.[5] Late potentials of this type are particularly sensitive to non-analgesic sedation, as seen in the morphine but not in the M-6-G or placebo groups in the study of Loetsch and colleagues.

Because of the difficulties of true blinding in opioid medication groups, we chose an open study design. The choice of tests for demonstration of opioid analgesia is crucial, as phasic, mainly A-δ fibre activating stimuli, as used by Loetsch and colleagues, have been shown to be insensitive for this purpose.[6] The tonic and suprathreshold pain tolerance tests in our study were chosen to ensure activation of C-fibres sensitive to opioid effects. Although qualitative responses to electrical and cold pain stimulation were similar, the former is a multimodal stimulus and the latter probably monomodal. Clinical studies with patients are now necessary to further evaluate the therapeutic potential of M-6-G.

Acknowledgements

This work was supported by the Bernese Office of Industry and Labour (project No. BEA1 97–815), the Institute of Medical Oncology and the Nociception Research Group of the University of Bern The gift of M-6-G by Lipomed is kindly acknowledged

References

1 Milne RW, Nation RL, Somogyi AA. The disposition of morphine and its 3- and 6-glucuronide metabolites in humans and animals, and the importance of the metabolites to the pharmacological effects of morphine. *Drug Metab Rev* 1996; **28**: 345–472
2 Thompson PI, Joel SP, John L, Wedzicha JA, Maclean M, Slevin ML. Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol* 1995; **40**: 145–52
3 Loetsch J, Kobal G, Stockmann A, Brune K, Geisslinger G. Lack of analgesic activity of morphine-6-glucuronide after short-term intravenous administration in healthy volunteers. *Anesthesiology*

1997; **87**: 1348–58

4 Bourquin D, Bundeli P, Lehmann T, Brenneisen R. Diacetylmorphine and its metabolites in plasma by HPLC with diode-array and atmospheric pressure ionization mass spectrometric detection *J Liquid Chromatogr Related Technol* (in press)

5 Zaslansky R, Sprecher E, Katz Y, Rozenberg B, Hemli JA, Yarnitsky D. Pain-evoked potentials: what do they really measure? *Electroencephalogr Clin Neurophysiol* 1996; **100**: 384–91

6 McCormack K, Prather P, Chapleo C. Some new insights into the effects of opioids in phasic and tonic nociceptive tests. *Pain* 1998; **78**: 79–98

British Journal of Anaesthesia 84 (1): 100–2 (2000)

Comparison of different doses of remifentanil on the cardiovascular response to laryngoscopy and tracheal intubation†

A. P. Hall, J. P. Thompson*, N. A. P. Leslie, A. J. Fox, N. Kumar and D. J. Rowbotham

University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK

**Corresponding author*

We have compared three bolus and infusion regimens of remifentanil on the cardiovascular response to laryngoscopy and orotracheal intubation in three groups of 20 ASA I–II female patients, in a randomized, double-blind study. Patients in group 1 received glycopyrrolate 200 μg i.v. followed by a bolus dose of remifentanil 1 μg kg^{-1} over 30 s and an infusion of remifentanil at a rate of 0.5 μg kg^{-1} min^{-1}. The other patients received remifentanil 0.5 μg kg^{-1} over 30 s and an infusion of 0.25 μg kg^{-1} min^{-1} with (group 2) or without (group 3) pretreatment with glycopyrrolate 200 μg. All patients then received a sleep dose of propofol, rocuronium 0.6 mg kg^{-1} and 1% isoflurane with 67% nitrous oxide in oxygen. Laryngoscopy and tracheal intubation were performed 3 min later. Heart rate and arterial pressure were recorded at 1-min intervals from before induction of anaesthesia until 5 min after intubation. Baseline heart rate was similar in all groups, but decreased in group 3 (no glycopyrrolate) after induction and remained significantly lower after intubation compared with the other groups ($P<0.05$). Heart rate and arterial pressure increased slightly after intubation in each group but there were no significant differences in mean arterial pressure between groups at any time. The incidence of bradycardia (one patient in group 2) and hypotension (two patients in groups 1 and 2 and three patients in group 3) was low.

Br J Anaesth 2000; **84**: 100–2

Keywords: analgesics opioid, remifentanil; premedication, glycopyrrolate; intubation tracheal, responses; cardiovascular system, effects

Accepted for publication: August 3, 1999

Laryngoscopy and tracheal intubation can cause tachycardia, hypertension, arrhythmias, increased plasma catecholamine concentrations and myocardial ischaemia in susceptible individuals.[1] These responses may be attenuated by i.v. opioids, vasodilators, calcium channel and β-blockers, or deepening of anaesthesia.[1] Remifentanil is a new opioid with a rapid onset (1–2 min) and short duration of effect, which makes it ideal for attenuation of brief but noxious stimuli. The dose of remifentanil recommended at induction of anaesthesia is 1 μg kg^{-1} followed by an infusion of 0.25–1.0 μg kg^{-1} min^{-1}.[2] We have shown previously that this dose attenuates the haemodynamic response to laryngoscopy and tracheal intubation in healthy adults.[3] However, bradycardia and hypotension occurred in five of 10 patients who did not receive pretreatment with glycopyrrolate and we postulated that a lower dose of remifentanil might be effective, without these side effects. We have therefore compared the haemodynamic response to laryngoscopy and tracheal intubation in patients receiving the recommended remifentanil regimen (with glycopyrrolate) or half this dose, both with and without glycopyrrolate pretreatment.

Methods and results

After obtaining approval from the Local Research Ethics Committee and informed written consent, we studied 60 ASA I–II female patients, aged 20–56 yr, presenting for elective surgery. Patients were allocated to one of three groups in a randomized, double-blind manner. The groups were: glycopyrrolate 200 μg i.v. followed by a bolus dose of remifentanil 1 μg kg^{-1} given over 30 s, and a subsequent infusion of remifentanil 0.5 μg kg^{-1} min^{-1} (group 1); and remifentanil 0.5 μg kg^{-1} given over 30 s and an infusion of remifentanil 0.25 μg kg^{-1} min^{-1} preceded by glycopyrrolate 200 μg (group 2) or saline (group 3). All drugs were prepared by an independent anaesthetist; the investigators were blinded to the identity of the drugs.

Immediately after the bolus dose of remifentanil, anaesthesia was induced with propofol 0.5 mg kg^{-1} followed by 10 mg every 10 s to loss of verbal contact, and rocuronium

---

†Presented in part to the Anaesthetic Research Society, University of Dundee, July 10, 1998 (*Br J Anaesth* 1998; **81**; 637P)

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Mean (SD) cardiovascular variables before and after induction of anaesthesia and laryngoscopy and intubation in group 1 (1 µg bolus/0.5 µg kg^{-1} min^{-1} infusion, glycopyrrolate pretreatment), group 2 (0.5 µg bolus/0.25 µg kg^{-1} min^{-1} infusion, glycopyrrolate pretreatment) and group 3 (0.5 µg bolus/0.25 µg kg^{-1} min^{-1} infusion, no glycopyrrolate) $^*P<0.05$ between groups

		After induction			After laryngoscopy and intubation				
	Baseline	**1 min**	**2 min**	**3 min**	**1 min**	**2 min**	**3 min**	**4 min**	**5 min**
Group 1 (*n*=20)									
SAP	125 (13)	111 (17)	100 (13)	94 (10)	105 (20)	100 (15)	96 (11)	93 (10)	93 (9)
MAP	88 (11)	77 (18)	67 (13)	62 (11)	73 (16)	69 (14)	65 (10)	54 (9)	62 (8)
DAP	72 (9)	62 (16)	56 (12)	50 (11)	61 (14)	57 (12)	53 (10)	52 (9)	51 (8)
HR	84 (17)	86 (17)	82 (15)	81 (15)	86 (16)	86 (17)	84 (16)	82 (15)	80 15)
Group 2 (*n*=20)									
SAP	127 (16)	110 (16)	98 (14)	92 (13)	109 (17)	102 (12)	94 (12)	92 (11)	91 (12)
MAP	91 (14)	75 (13)	66 (12)	59 (11)	75 (13)	71 (10)	64 (10)	62 (10)	61 (10)
DAP	76 (11)	62 (13)	53 (11)	47 (9)	63 (13)	58 (9)	52 (8)	48 (9)	50 (10)
HR	85 (12)	86 (15)	85 (13)	81 (16)	90 (17)	86 (15)	83 (15)	81 (15)	78 (15)
Group 3 (*n*=20)									
SAP	123 (13)	108 (13)	99 (9)	92 (9)	102 (12)	97 (11)	94 (9)	91 (9)	89 (8)
MAP	88 (10)	75 (11)	64 (7)	60 (8)	71 (11)	65 (8)	61 (8)	58 (8)	57 (7)
DAP	76 (10)	63 (13)	53 (8)	47 (7)	60 (12)	54 (9)	49 (8)	46 (7)	46 (7)
HR	77 (13)	77 (12)	72 (12)	69 (11)*	79 (15)	73 (13)*	69 (12)*	65 (12)*	63 (11)*

0.6 mg kg^{-1}. Patients' lungs were ventilated manually with 1% isoflurane with 67% nitrous oxide in oxygen until intubation, and mechanically thereafter using a Manley ventilator (tidal volume 10 ml kg^{-1}, end-tidal carbon dioxide partial pressure 4.0–4.5 kPa). Arterial pressure was measured non-invasively by an automatic oscillometer (Datex Cardiocap) and heart rate was recorded from the ECG trace. Intubation was performed 3 min after induction of anaesthesia.

Heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were recorded at 1-min intervals from before induction of anaesthesia to 5 min after intubation. Hypotension (SAP <80 mm Hg for >60 s) was treated with increments of ephedrine 3 mg i.v. or atropine 300 µg i.v. (if HR <50 beat min^{-1}). Bradycardia (HR <45 beat min^{-1} for >60 s) was treated with atropine in increments of 300 µg.

Power calculations based on our previous data[3] showed that 20 patients per group would be required to demonstrate a difference in MAP of 15 mm Hg or HR of 15 beat min^{-1} (α=0.05, β=0.1), or a reduction in the incidence of bradycardia or hypotension to 10% (α=0.05, β=0.2). Statistical analysis was performed using two-way and multivariate analysis of variance for repeated measures (ANOVA, MANOVA with treatment group and time as the between- and within-group factors) and paired and unpaired *t* tests with Bonferroni post-test analysis as appropriate using SPSS for Windows computer software (release 6.0, 1993).

Mean ages were 34.4 (range 21–45) yr, 35.3 (24–56) yr and 32.1 (20–48) yr in groups 1, 2 and 3, respectively. Mean weights were 67.6 (SD 11.6) kg, 69.2 (15.3) kg and 65.9 (15.7) kg, and propofol doses were 1.97 (0.46) mg kg^{-1}, 2.01 (0.42) mg kg^{-1} and 2.04 (0.54) mg kg^{-1} in the three groups, respectively. Baseline SAP, MAP, DAP and HR were similar (Table 1). Heart rate decreased in group 3 after induction of anaesthesia and remained lower after tracheal intubation compared with the other groups ($P<0.05$). MAP increased by 11–16 mm Hg and mean HR increased by 6–11 beat min^{-1} after intubation, but within- or between-group differences in arterial pressure (SAP, MAP and DAP) were not statistically significant. Hypotension requiring escape medication occurred in two patients in groups 1 and 2 and in three patients in group 3. One patient in group 2 developed bradycardia requiring treatment.

Comment

We found no difference between a bolus dose of remifentanil 0.5 µg kg^{-1} followed by an infusion of 0.25 µg kg^{-1} min^{-1} and twice these doses in attenuating the potential cardiovascular responses to laryngoscopy and orotracheal intubation. Heart rate decreased after induction of anaesthesia in patients who did not receive glycopyrrolate, and remained significantly lower compared with the two other groups. However, the only episode of bradycardia that fulfilled our criteria for escape medication occurred in a patient who received glycopyrrolate at induction (group 2).

A study in similar patients, using propofol, vecuronium 0.5 mg kg^{-1} and a bolus dose of remifentanil 1 µg kg^{-1} followed by an infusion of 0.5 µg kg^{-1} min^{-1}, found that remifentanil was associated with bradycardia or hypotension in five of 10 patients, compared with one of 10 in the group that also received glycopyrrolate 200 µg.[3] After a change in hospital pharmacy policy, the neuromuscular blocking drug used in the present study was rocuronium 0.6 mg kg^{-1}, which has a mild vagolytic effect and is associated with a lower incidence of bradycardia than vecuronium.[4] However, mean MAP and HR immediately before laryngoscopy in the previous study were 59 mm Hg and 80 beat min^{-1}, which were very similar to the corresponding values reported here, despite the use of rocuronium.

McAtamney and colleagues reported that after thiopental 5–7 mg kg^{-1}, a bolus dose of remifentanil 1 µg kg^{-1} was more effective in reducing the pressor response to intubation and resulted in a more rapid return to baseline values of heart rate and arterial pressure than 0.25 or 0.5 μg kg^{-1}.[5] It is unclear if thiopental was titrated to effect. Heart rate increased in all treatment groups after induction of anaesthesia and increased further after laryngoscopy and intubation. Two of 20 patients in the remifentanil 1 μg kg^{-1} group became hypotensive, although their heart rates were not reported separately.

The same group examined the effect of remifentanil 0.5, 1.0 or 1.25 μg kg^{-1} on haemodynamic changes during rapid sequence induction of anaesthesia with thiopental 5–7 mg kg^{-1} and succinylcholine 1.0 mg kg^{-1}.[6] Remifentanil 0.5 μg kg^{-1} was ineffective in controlling the pressor response but SAP was less than 90 mm Hg in seven of 20 patients receiving remifentanil 1.25 μg kg^{-1}.

The differences between these studies and ours may be related to administration of thiopental 5–7 mg kg^{-1} before the bolus dose of remifentanil. The use of a bolus–infusion technique results in a rapid, stable concentration of remifentanil, and is logical when remifentanil is to be continued during operation. Remifentanil given before induction of anaesthesia decreases the required dose of i.v. anaesthetic agent, and propofol was titrated to loss of verbal contact in this study. The pressor response reaches a peak 1–2 min after laryngoscopy and intubation, and usually subsides within 5–6 min, although tachycardia may persist for 10 min.[7] The effect-site half-life of a remifentanil bolus is only 3.2 min, and the use of a bolus–infusion regimen is therefore rational, as acknowledged previously.[5]

This type of study may be criticized as the patients recruited were not at risk of haemodynamic responses, and no information regarding outcome was given.[8] However, we felt it important to establish the most effective regimen for remifentanil at induction of anaesthesia, especially in view of previous reports of bradycardia, before extending this work to higher risk groups. The results from this and the previous study[3] suggest that the recommended dose is excessive in healthy patients.

In summary, we observed only slight changes in heart rate and arterial pressure after laryngoscopy and tracheal intubation when remifentanil 0.5 μg kg^{-1} i.v. given over 30 s followed by an infusion of 0.25 μg kg^{-1} min^{-1} was used as part of a balanced anaesthetic technique at induction of anaesthesia in healthy adults. Heart rate was lower in patients who did not receive glycopyrrolate, but only one patient who had received glycopyrrolate developed bradycardia requiring treatment. Hypotension requiring escape medication occurred in two patients in groups 1 and 2 and in three patients in group 3.

References

1 Kovac AL. Controlling the hemodynamic response to laryngoscopy and endotracheal intubation. *J Clin Anesth* 1996; **8**: 63–79

2 *ABPI Compendium of Datasheets 1998–99*. London: Datapharm Publications Ltd, 1998

3 Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ. Effect of remifentanil on the haemodynamic response to orotracheal intubation. *Br J Anaesth* 1998; **80**: 467–9

4 McCoy EP, Maddineni VR, Elliott P, Mirakhur RK, Carson IW, Cooper RA. Haemodynamic effects of rocuronium during fentanyl anaesthesia: comparison with vecuronium. *Can J Anaesth* 1993; **40**. 703–8

5 McAtamney D, O'Hare R, Hughes D, Carabine U, Mirakhur R. Evaluation of remifentanil for control of haemodynamic response to tracheal intubation. *Anaesthesia* 1998; **53**: 1223–7

6 O'Hare R, McAtamney D, Mirakhur RK, Hughes D, Carabine U. Bolus dose remifentanil for control of haemodynamic response to tracheal intubation during rapid sequence induction of anaesthesia. *Br J Anaesth* 1999; **82**: 283–5

7 Singh H, Vichitvejpaisal P, Gaines GY, White PF. Comparative effects of lidocaine, esmolol, and nitroglycerin in modifying the hemodynamic response to laryngoscopy and intubation. *J Clin Anesth* 1995; **7**: 5–8

8 Thomson IR. The haemodynamic response to intubation: a perspective. *Can J Anaesth* 1989; **36**: 367–9

British Journal of Anaesthesia **84** (1): 103–5 (2000)

Comparison of laryngeal mask and intubating laryngeal mask insertion by the naïve intubator

A. Choyce[1]*, M. S. Avidan[1], C. Patel[1], A. Harvey[1], C. Timberlake[1], N. McNeilis[1] and E. Glucksman[2]

[1]Department of Anaesthesia and [2]Department of Accident and Emergency, King's College Hospital, Denmark Hill, London SE5 9RS, UK

**Corresponding author*

Seventy-five inexperienced participants were timed inserting the laryngeal mask airway (LMA) and the intubating laryngeal mask (ILM) in one of five cadavers. Adequacy of ventilation was assessed on a three-point scale depending on chest expansion and air leak. Participants were also asked to intubate the trachea via the ILM. The ILM was inserted faster than the LMA ($P<0.05$) with a greater proportion achieving adequate ventilation after their first attempt ($P<0.05$). Tracheal intubation via the ILM was completed successfully by 67% (52 of 75) of participants. In a questionnaire, participants stated that the ILM was easier to use and the preferred device in an emergency. The results suggest that inexperienced practitioners should use the ILM rather than the LMA for emergency ventilation.

Br J Anaesth 2000; **84**: 103–5

Keywords: intubation tracheal; intubation tracheal, training; equipment, masks anaesthesia

Accepted for publication: August 31, 1999

Studies have shown that unskilled personnel insert the laryngeal mask airway (LMA) more rapidly and reliably than a tracheal tube[1] and that it provides better ventilation than a face mask.[2] The 1998 European Resuscitation Council guidelines for adult advanced life support state that the tracheal tube remains the gold standard for securing the airway but that the LMA offers an alternative.[3]

A new device is now available, the intubating laryngeal mask (ILM). This is a modified form of the LMA designed as a conduit for tracheal intubation The success rate for intubation via the ILM has been estimated at 93%.[4] But in the hands of those inexperienced in advanced airway management, the ILM failed to increase the chance of successful tracheal intubation compared with direct laryngoscopy.[5] The same study showed that in common with the LMA, ventilation with the ILM was superior to ventilation with a face mask.

During resuscitation, the ILM can be inserted by a non-anaesthetist and used to ventilate the patient's lungs until an experienced airway practitioner arrives. Valuable time could be saved if the tracheal tube was then passed through the ILM, circumventing the need for direct laryngoscopy under difficult conditions. In this study, we have compared the ILM with the LMA in a simulated resuscitation context, where those managing the airway were not trained in advanced airway management.

Methods and results

Participants in the study were 75 medical students without anaesthetic experience The Local Ethics Committee approved the study and informed consent was obtained from relatives of five recently deceased cadavers. Investigators were anaesthetists with clinical experience of both devices. Participants were trained to insert both devices on the airway management training manikin (Laerdal) and through demonstration on a cadaver. Participants were considered trained when they achieved two sequential successful manikin insertions with each device.

Each participant then inserted both devices, one immediately after the other, in a random sequence (after the toss of a coin) into a single cadaver placed in the supine position with the head supported by the equivalent of a small pillow. A size 4 device was used for female cadavers and a size 5 for males. To standardize cuff inflation volume, the recommended maximum was used. The time taken from first handling the device to insertion and attaching a self-inflating bag was recorded. Ventilation was then attempted and graded by two investigators as either poor (large leak, minimal or no ventilation), moderate (some leak but adequate ventilation) or good (minimal or no leak and adequate ventilation). Adequate ventilation was taken as visible chest expansion. If a participant failed to achieve adequate ventilation (i.e. moderate or good) then a second and final attempt at insertion was allowed.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

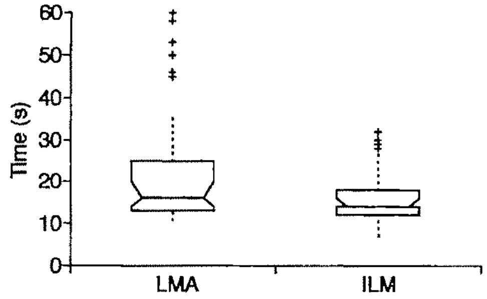


Fig 1 Time to insertion of the laryngeal mask airway (LMA) and the intubating laryngeal mask (ILM). LMA. median 16 s, interquartile range (IQR) 13–25 s, range 9–120 s ILM· median 14 s, IQR 12–18 s, range 7–65 s. The broken lines represent 1.5 times IQR, + represents participants whose time to insertion exceeded 1.5 times IQR but was less than 60 s.

Each participant then attempted tracheal intubation with an 8-mm Euromedical ILM tracheal tube using the ILM they had sited as a conduit. Two investigators assessed success at intubation by observation and auscultation of the chest. One investigator, using the same ILM placement, repeated the attempt at intubation. Finally, participants completed a questionnaire assessing their views on the two devices.

Data were analysed on an AEC P300 personal computer using Analyse-It for Microsoft Excel from Analyse-It Software Ltd. The Wilcoxon rank sum test was used to compare the time to insertion of each device. Fisher's exact test was used to compare adequacy of ventilation and evaluate participants' responses to the questionnaire. $P<0.05$ was regarded as significant.

Figure 1 shows box and whisker plots for time to insertion at the first attempt with each device. The ILM was inserted significantly faster than the LMA ($P<0.05$). The median reduction in time from first handling the device to insertion and attachment of a self-inflating bag was 3.5 s (95% confidence interval (CI) 1.5–6 s).

The likelihood of adequate ventilation after first insertion of the ILM was 92% (69 of 75) compared with 76% (57 of 75) with the LMA. This 16% difference was statistically significant ($P<0.05$, 95% CI 4.5–27.5%). A comparison of ventilation was made between the devices after one or, if indicated, two attempts at insertion. The likelihood of adequate ventilation (moderate or good) with the ILM was 89% (72 of 81) compared with 71% (65 of 91) with the LMA. This 18% difference was statistically significant ($P<0.05$, 95% CI 5.9–29.0%). Similarly, the likelihood of good as opposed to moderate or poor ventilation with the ILM was 58% (47 of 81) compared with 30% (27 of 91) with the LMA. This 28% difference was statistically significant ($P<0.05$, 95% CI 14.1–42.6%). When asked to attempt tracheal intubation via the ILM, this was completed successfully by 67% (52 of 75) of participants. The attending investigator achieved 95% (71 of 75) success.

All but three participants completed the questionnaire.

1. (1) Which device did you find easier to use? Forty-four said the ILM; eight the LMA ($P<0.05$); and 20 both the same.
2. (2) Would you feel confident using these devices in an emergency situation? ILM: 64 yes; eight no. LMA: 53 yes; 19 no.
3. (3) Offered a choice of device in an emergency, which device would you choose? ILM 53; LMA 17 ($P<0.05$); two said either.

Comment

We have shown that the ILM was inserted significantly faster than the LMA in the hands of the naïve intubator. A reduction in the median insertion time of 3.5 s, although statistically significant, appears to have limited clinical relevance. However, we have shown additional advantages of the ILM; it provided superior ventilation and was the preferred device among participants.

Unlike intubation of the trachea, the technique of LMA insertion is easily taught to nurses, paramedics and doctors.[2] This has led to the suggestion that the LMA should be used as a first-line airway adjunct for those who do not have the skill to intubate the trachea.[3] Our results suggest that the ILM may be more useful than the LMA in emergency resuscitation. But data from this and a previous study do not support the use of the ILM as a conduit for tracheal intubation by the non-anaesthetist.[5] However, the results of both studies strongly suggest that inexperienced practitioners may use the ILM for ventilation.

Use of the ILM in the management of the difficult airway and during manual in-line neck immobilization shows that its role in anaesthetic practice is evolving. Experience of tracheal intubation with this device in manikins has been shown to be a poor predictor of success in patients.[5] We accept the limitations of performing this study on a relatively small number of cadavers but our results have led us to undertake a similar study on anaesthetized patients. If anaesthetists are to gain the experience necessary to achieve a high success rate at intubation with the ILM, it may be prudent to obtain it on cadavers before using it on anaesthetized patients.[6]

Acknowledgements

Intavent Ltd provided the ILMs used in this study. We thank Mrs E. Packham (relative liaison officer at King's College Hospital) for gaining consent from the relatives of the deceased

References

1 Pennant JH, Walker MB. Comparison of the endotracheal tube and laryngeal mask in airway management by paramedical personnel. *Anesth Analg* 1992; **74**: 531–4

2 Martin PD, Cyna AM, Hunter WAH, Henry J, Ramayya GP. Training nursing staff for resuscitation—a clinical comparison of the facemask and laryngeal mask. *Anaesthesia* 1993; **48**: 33–7

3 The 1998 European Council guidelines for adult advanced life support. Advanced Life Support Working Group of the European Resuscitation Council *BMJ* 1998; **316**: 1863–9

4 Kapila A, Addy EV, Verghese C, Brain AIJ. The intubating laryngeal mask airway: an initial assessment of performance. *Br J Anaesth* 1997; **79**: 710–13

5 Avidan MS, Harvey A, Chitkara N, Ponte J. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth* 1999; **83**; 615–17

6 Branthwaite MA. An unexpected complication of the intubating laryngeal mask. *Anaesthesia* 1999; **54**:166–7

British Journal of Anaesthesia 84 (1): 106–7 (2000)

Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment

K. F. Cheong* and W. H. Wong

Department of Anaesthesia, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074, Singapore

**Corresponding author*

We have assessed the incidence of pain on injection of rocuronium and evaluated if pretreatment with lidocaine i.v. reduced it, in a randomized, controlled study in 90 patients. We found that 37% of patients who received lidocaine 10 mg pretreatment had pain on injection of rocuronium compared with 77% of patients who received saline pretreatment and 7% of patients who were pretreated with lidocaine 30 mg ($P<0.05$ in each instance compared with control). In addition, patients pretreated with lidocaine were less likely to suffer moderate or severe pain. Both lidocaine 10 mg and 30 mg i.v. given before administration of rocuronium significantly reduced the incidence and severity of pain on injection of rocuronium, and the higher dose was more effective.

Br J Anaesth 2000; **84**: 106–7

Keywords: neuromuscular block, rocuronium; anaesthetics local, lidocaine; pain, injection

Accepted for publication: August 31, 1999

Rocuronium is given in precurarization, timing or priming techniques before induction of anaesthesia.[1 2] (The timing principle entails administration of a single bolus dose of a non-depolarizing neuromuscular blocking agent followed by an induction drug at the onset of clinical weakness.) The incidence of pain on injection of rocuronium is high; reports suggest that 50–80% of patients suffer pain.[3 4] The aim of this study was to examine the incidence of pain on injection of rocuronium and to evaluate if prior administration of lidocaine 10 mg or 30 mg i.v. decreased the incidence and severity of injection pain.

Methods and results

After obtaining approval from the Institutional Ethics Committee and informed consent, we studied 90 ASA I–II patients undergoing a variety of orthopaedic and general surgical procedures requiring general anaesthesia with positive pressure ventilation. Patients were allocated randomly to one of three groups: lidocaine 10 mg, lidocaine 30 mg or placebo (control). Those with difficult venous access or requiring rapid sequence induction were excluded. Patients were informed that they would be receiving a drug at the start of their anaesthetic that may make their arm 'sting'. They were told that they would be asked to score the pain, if any occurred, after the drug had been given. No premedication was given.

On arrival in the operating room, a 22-gauge cannula was placed in the largest vein on the dorsum of the hand without the use of local anaesthesia. All patients were monitored with an electrocardiograph, pulse oximeter and an automatic non-invasive arterial pressure monitor. Patients were allocated randomly using sealed envelopes to receive isotonic saline (control group), lidocaine 10 mg or lidocaine 30 mg at ambient temperature (20–24°C). All syringes were prepared by another investigator and covered so that the investigator who assessed the patient's response was unaware of the nature of the solution. Ten seconds after injection of the pretreatment drug, an intubating dose of rocuronium 0.6 mg kg^{-1} at room temperature was injected over 10–15 s. The patient was asked during this period if his arm was comfortable and to report the severity of any pain on a four-point scale (none, mild, moderate, severe). Thirty seconds after administration of rocuronium, propofol was administered i.v. until loss of consciousness and anaesthesia proceeded as planned.

Based on an estimated incidence of approximately 80% of patients experiencing pain on injection of rocuronium, the sample size required to detect a 50% reduction at a level of significance of 5% and a power of 90% was 30 patients per group. Patient characteristics were compared using the Student's t test. The chi-square test was used to compare the incidence of pain in the three groups. Results were considered significant when $P<0.05$.

There were no differences in patient characteristics between the three groups in terms of mean age (control 34.9 (range 20–58) yr; lidocaine 10 mg 36.9 (18–62) yr; lidocaine 30 mg 37.7 (20–55) yr), sex distribution (control

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Incidence and characteristics of pain on injection of rocuronium Results are expressed as number of patient responses. *$P<0.05$ compared with control, †$P<0.05$, lidocaine 30 mg compared with lidocaine 10 mg (chi-square)

	Control ($n=30$)	Lidocaine 10 mg ($n=30$)	Lidocaine 30 mg ($n=30$)
None	7	19*	28*†
Mild	5	4	0
Moderate	11	4	2*
Severe	7	3	0*

20 males/10 females; lidocaine 10 mg 22 males/eight females; lidocaine 30 mg 17 males/13 females) or mean body weight (control 66.8 (SD 12.5) kg; lidocaine 10 mg 63.2 (15.2) kg; lidocaine 30 mg 64.8 (10.5) kg). Twenty-three of 30 patients in the control group had pain on injection of rocuronium (76.7%). Both lidocaine groups had significantly lower incidences of pain compared with the control group. Eleven of 30 patients (37%) in the lidocaine 10 mg group had pain on injection of rocuronium, which was significantly greater than the two of 30 patients (7%) in the lidocaine 30 mg group ($P<0.05$) (Table 1). In addition, patients who were pretreated with lidocaine 30 mg before administration of rocuronium were less likely to suffer moderate or severe pain than those in the control group ($P<0.05$).

Comment

Pain associated with injection of rocuronium is common and can be very distressing. In our study, several patients described the pain as 'burning' in nature and occurred immediately on administration. We do not know the exact mechanism for the pain, although the immediate onset probably reflects a direct irritant effect and not an indirect effect on the kinin cascade. Klement and Arndt[5] showed that acidic and alkaline solutions elicited pain at pH values less than 4 and more than 11, respectively. Pain latency also decreased with increasing osmolality, acidity and alkalinity. They postulated that pain is caused by the unphysiological osmolality or pH of the formulations. Rocuronium is supplied as an isotonic solution with a pH of 4. Injection pain is probably caused by the low pH.

Information in the packet insert suggests that lidocaine pretreatment may be effective in attenuating pain on injection, without alluding to the efficacy of this modality. We have examined the efficacy of lidocaine pretreatment, which was found to be effective in obtunding the pain associated with injection of propofol.[6] Our data showed that the incidence of pain on injection of rocuronium was reduced significantly from 77% to 37% ($P<0.001$) when lidocaine 10 mg was given before rocuronium, and was reduced further to 7% when lidocaine 30 mg was given. The number of patients who complained of moderate and severe pain in the lidocaine 30 mg group was significantly smaller than that in the control group. A smaller incidence of moderate and severe pain in the lidocaine 10 mg group compared with the control group was also seen, although this was not statistically significant. A dose-dependent effect of lidocaine in attenuating pain was present. While our study examined only two doses of lidocaine pretreatment, perhaps a higher dose (such as 50 mg) may completely abolish rocuronium injection pain.

Pain on injection of rocuronium is significant and perhaps other clinical strategies could be developed to prevent it. Rocuronium is an invaluable addition to our practice, allowing more rapid tracheal intubation. Attenuation of the pain caused by its injection could make it less distressing for the patient to receive, and improve the quality of induction and acceptability of this otherwise useful agent.

References

1 Sieber TJ, Zbinden AM, Curatolo M, Shorten GD. Tracheal intubation with rocuronium using the 'timing principle'. *Anesth Analg* 1998; **86**. 1137–40

2 Tsui BC, Reid S, Gupta S, Kearney R, Mayson T, Finucane B. A rapid precurarization technique using rocuronium *Can J Anaesth* 1998; **45**: 397–401

3 Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: Is pain on injection the cause? *Br J Anaesth* 1997; **79**: 382–3

4 Steegers MA, Robertson EN. Pain on injection of rocuronium bromide. *Anesth Analg* 1996; **83**: 203

5 Klement W, Arndt JO. Pain on intravenous injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *Br J Anaesth* 1991; **66**: 189–95

6 Tan CH, Onsiong MK. Pain on injection of propofol. *Anaesthesia* 1998; **53**: 468–76

British Journal of Anaesthesia 84 (1): 108–11 (2000)

BJA

CASE REPORTS

Histaminoid reactions associated with rocuronium

S. McD. Neal, P. R. Manthri, V. Gadiyar[1] and J. A. W. Wildsmith

Department of Anaesthesia, Ninewells Hospital, Dundee DD1 9SY, UK

[1]Present address: Department of Anaesthesia, Fairfield General Hospital, Bury, Lancashire BL9 7TD, UK

We describe three histaminoid reactions occurring on induction of anaesthesia. The patients were all resuscitated successfully and subsequent skin testing suggested sensitivity to rocuronium. In this hospital, the incidence of such reactions is of the order of 1 in 3000. This may be coincidental but suggests that there should be close monitoring of the incidence of reactions to rocuronium. Review of the cases suggests that current guidelines on management are not always followed.

Br J Anaesth 2000; **84**: 108–11

Keywords: histamine; neuromuscular block, rocuronium; complications, anaphylaxis

Accepted for publication: August 4, 1999

Rocuronium is a monoquaternary aminosteroid neuromuscular blocking agent which first became available in 1994.[1] Its main advantage is rapid onset, a dose of 0.6 mg kg^{-1} producing block at the adductor pollicis muscle in 60–90 s.[2 3] In common with vecuronium, another member of the aminosteroid group, rocuronium has been shown to cause less histamine release and cardiovascular instability than the benzylisoquinolinium neuromuscular blocking agents such as atracurium and mivacurium.[4] However, it retains the potential to act as an antigen and three acute reactions have occurred in association with its use in our hospital in the past 2 yr. Skin testing suggested that each of these reactions was caused by rocuronium. We are aware of only one other published report,[5] and therefore we felt it appropriate to draw attention to these cases and to review their management.

Case reports

Patient No. 1

A 58-yr-old woman was undergoing laparoscopic cholecystectomy after an episode of acute cholecystitis. She had a past history of palpitations for which she was receiving atenolol, although cardiological investigations, including a 24-h tape and exercise tolerance test, were negative. Previous general anaesthesia for a gynaecological procedure (thiopental 325 mg, atracurium 35 mg, morphine 7.5 mg, nitrous oxide, oxygen and enflurane) had been uneventful.

The patient was not premedicated. In the anaesthetic room, standard monitoring was commenced and i.v. access secured. Arterial pressure (non-invasive) was 100/46 mm Hg and heart rate 60 beat min^{-1}. The lungs were preoxygenated and anaesthesia was induced with morphine 5 mg i.v. and propofol 130 mg i.v. Rocuronium 40 mg was also given i.v. and, before intubation, the lungs were ventilated by hand with oxygen, nitrous oxide and isoflurane using a face mask, Guedel airway and a 'Humphrey ADE' circuit.

Some difficulty in lung ventilation was noted, with inflation pressures greater than expected being required to produce chest movement. A grade I view was obtained at laryngoscopy and the trachea was intubated with an 8-mm cuffed tracheal tube. The patient was noted to be generally erythematous, but with central cyanosis (oxygen saturation 86%) and an arterial pressure of 56/26 mm Hg. Auscultation of the chest revealed widespread wheeze.

Treatment for presumed anaphylaxis was commenced. The lungs were ventilated with 100% oxygen, epinephrine 1:10 000 was given i.v. in 1-ml increments (total 6 ml), and plasma protein solution (4.5% Alba) 800 ml i.v. was also given. Bronchospasm improved but methoxamine was given in 2-mg increments (total 20 mg) because the patient remained hypotensive and tachycardic. Chlorpheniramine 10 mg and hydrocortisone 200 mg were also given i.v. An arterial line, urinary catheter and an 8.5-French gauge right internal jugular venous line were inserted. Marked facial oedema was noted. Arterial blood-gas values revealed a pH of 7.19 with a base deficit of 9.7.

Fifty minutes after induction, the patient had stabilized with a heart rate of 99 beat min $^{-1}$, arterial pressure of 96/60 mm Hg and oxygen saturation of 98% on artificial

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

ventilation with 0.5% isoflurane in 100% oxygen. A total of 1600 ml of colloid and 2000 ml of crystalloid had been administered. The patient was transferred to the intensive care unit where she remained stable until the tracheal tube was removed 5 h later. Blood was analysed for serum tryptase 1 h after the reaction had occurred. Concentrations were increased at 95 ng ml^{-1} (normal <1–2 ng ml^{-1}), confirming that mast cell degranulation had occurred.

The patient returned for skin testing 4 weeks later. Non-invasive monitoring (ECG, arterial pressure and pulse oximetry) was commenced, i.v. access secured and written consent obtained. Prick testing to normal saline, 1% propofol, morphine 1 mg ml^{-1}, succinylcholine 50 mg ml^{-1} and atracurium 10 mg ml^{-1} was uneventful. However, the patient complained of sensations of itch and burning almost instantly when rocuronium in 1:100 and 1:10 dilutions (0.1 mg ml^{-1} and 1 mg ml^{-1}, respectively) were applied. A wheal <5 mm in diameter appeared in response to rocuronium 0.1 mg ml^{-1}, and one >5 mm in response to rocuronium 1 mg ml^{-1}. There was also a positive reaction to vecuronium, less intense than that to rocuronium. Subsequent administration of propofol, fentanyl, atracurium and morphine was uneventful.

Patient No. 2

A 29-yr-old woman with a history of hay fever for which she took no medication was undergoing laparoscopic sterilization. Her health was good and she had twice undergone uneventful general anaesthesia (atropine 0.6 mg, midazolam 2 mg, fentanyl 0.1 mg, propofol 100 mg, nitrous oxide, oxygen and enflurane; and fentanyl 0.05 mg, propofol 160 mg, nitrous oxide, oxygen and isoflurane) for minor surgical procedures in the past. Venous access was secured and standard monitoring instituted. Arterial pressure was 110/70 mm Hg and heart rate was 85 beat min^{-1}.

Anaesthesia was induced with propofol 170 mg, fentanyl 0 1 mg, glycopyrrolate 0.2 mg and rocuronium 15 mg. Manual ventilation with a face mask was performed with 1.5% isoflurane in 33% oxygen and 66% nitrous oxide. Some difficulty with ventilation and a tachycardia of 140–150 beat min^{-1} were noted. A size 4 laryngeal mask airway was inserted as planned, but lung ventilation was difficult and auscultation of the chest revealed severe wheeze. The trachea was intubated with an 8-mm cuffed tracheal tube and manual ventilation was continued with 1% isoflurane in 100% oxygen. Within 3 min of induction, systolic arterial pressure was 45 mm Hg and Sp_{O_2} 85%. An erythematous rash developed over the whole body, but was more pronounced in the lower half.

Hartmann's solution 1 litre was infused rapidly and aminophylline 250 mg was given i.v., but bronchospasm improved only slightly. Therefore, epinephrine 0.3 mg was given slowly i.v, after which bronchospasm improved markedly. Plasma protein solution (Alba 4 5%) 2 litre was given over the next 30 min. Hydrocortisone 100 mg i.v. was also given. An arterial line was inserted and arterial blood-gas values showed a pH of 7.22 with a base deficit of 7.5. Arterial pressure improved to 90/50 mm Hg and Sp_{O_2} to 100%. A further dose of epinephrine 0.2 mg was given slowly i.v. after which ventilation was improved and no wheeze was audible on auscultation of the chest. The proposed surgery was abandoned. Forty minutes after induction of anaesthesia, the patient was stable, making respiratory efforts and opening her eyes. The trachea was extubated soon after and the patient was monitored in the recovery area with no subsequent problems. Blood samples were obtained but were not analysed for serum tryptase as requested.

Six weeks later the patient returned for skin prick testing as described above. This was positive for both rocuronium (1:10 dilution) and vecuronium (1:10 dilution) There was no reaction to atracurium or succinylcholine. Subsequent administration of spinal anaesthesia with hyperbaric 0.5% bupivacaine 2.5 ml and fentanyl 0.025 mg i.v. was uneventful.

Patient No. 3

A 40-yr-old man who suffered from gastro-oesophageal reflux was admitted for elective endoscopic sinus surgery. He was otherwise healthy and his only medication was ranitidine. Previous anaesthesia with fentanyl 0.1 mg, thiopental 450 mg, vecuronium 10 mg, nitrous oxide, oxygen and enflurane had been uneventful. After venous access was secured and standard monitoring commenced, a modified rapid sequence induction was performed The patient was given midazolam 2 mg, propofol 300 mg, fentanyl 0.1 mg and rocuronium 50 mg The trachea was intubated with a 9-mm cuffed tracheal tube and the lungs ventilated with isoflurane in oxygen and nitrous oxide. He was noted to have a tachycardia of 175 beat min^{-1} and to be markedly erythematous. Auscultation revealed wheeze throughout the chest, although oxygen saturation remained good throughout. Arterial pressure remained stable. Chlorpheniramine 10 mg and aminophylline 250 mg were given i v. and bronchospasm improved Surgery was postponed and the patient's lungs were ventilated with isoflurane in oxygen and nitrous oxide until a spontaneous ventilatory pattern had been re-established. The tracheal tube was removed approximately 1 h after induction of anaesthesia when the patient was awake.

Four weeks later the patient returned for skin prick testing as described above. This was positive for rocuronium (1:10 dilution). There was no reaction to atracurium, vecuronium, succinylcholine, midazolam or propofol. Subsequent anaesthesia with propofol, atracurium, fentanyl, nitrous oxide, oxygen and isoflurane was uneventful.

Discussion

Anaphylaxis is a type 1 hypersensitivity reaction, mediated by IgE, in which a foreign substance produces an exaggerated immunological response leading to release of vasoactive substances such as histamine and serotonin from basophils and mast cells. The clinical consequences of the release of these mediators may include pruritus, erythema, flushing, bronchospasm, hypotension and cardiovascular collapse. The term anaphylactoid is used to describe reactions that may be clinically indistinguishable from anaphylaxis but are not mediated by IgE.[6] Clearly distinguishing between anaphylactic and anaphylactoid reactions is difficult, which is why we have used the term 'histaminoid'.[7]

Estimates of the incidence of these reactions in anaesthesia vary from 1 in 350 to 700 in the UK,[8] to 1 in 20 000 in Australia.[9] Diagnosis may be difficult because the clinical features of an allergic reaction can be masked during anaesthesia, and cardiovascular instability or bronchospasm may be mistakenly attributed to other causes.[7] Prompt treatment is essential, but fortunately it is primarily supportive, although an approach open to the possibility of misdiagnosis is required. Of the drugs used in anaesthesia, neuromuscular blocking agents are the most frequently implicated, accounting for approximately 70% of allergic reactions.[10] Cross-reactivity between neuromuscular blocking agents is said to be common because of the ubiquitous quaternary ammonium group in these compounds, although rocuronium has been shown to exhibit less cross-reactivity than other neuromuscular blocking agents.[11] However, only two of our patients had been exposed to a neuromuscular blocking drug previously (patient No.1 atracurium, patient No. 3 vecuronium), but two subsequently responded positively to vecuronium.

In all of our three patients the diagnosis of an histaminoid event was evident, each exhibiting the classical features of cardiovascular, respiratory and dermal involvement. They varied in severity, with patient Nos 1 and 2 being typical of moderately severe reactions, while the third was less severe. Treatment guidelines have been published by the Association of Anaesthetists[12] and are available in all operating theatres in our hospital. Epinephrine is recommended as the mainstay of treatment but was given as a first-line drug in the treatment of only one of our patients. In patient No. 2, it was not given until bronchospasm had failed to respond to aminophylline. In the third case, which was less severe, none was given. This suggests that current guidelines were not followed; there was some reluctance to administer epinephrine even when the diagnosis of anaphylaxis was clearly suspected. In spite of this, all patients were treated successfully. This suggests that an expectant approach to treatment is not inappropriate in less severe cases, although our experience clearly supports the efficacy of epinephrine in severe cases. However, a drug with pure alpha agonist activity (methoxamine) was required in patient No. 1 to maintain arterial pressure and decrease heart rate, indicating the need for treatment to be matched to the clinical picture.

The guidelines from the Association of Anaesthetists recommend that the patient who has had a suspected anaphylactic reaction should be investigated in consultation with an allergist or a clinical immunologist. However, ready access to such specialists may, as in our hospital, be difficult, and skin testing was performed under the supervision of an anaesthetist with experience in its interpretation. It might be argued that any large centre should have an anaesthetist with this interest, because an anaesthetist has the appropriate skills to resuscitate the patient should skin testing precipitate a systemic response. An anaesthetist will also have a greater awareness of the other factors that may cause problems on induction of anaesthesia. Involvement of anaesthetists in testing should also increase awareness of the specifics of the process for the drugs used by the specialty. This is not irrelevant to this report. Having tested all of these patients, we found that there was some evidence that the 'steroid' neuromuscular blocking drugs should be tested in a dilution starting at 1:100, rather than the 1:10 dilution currently recommended.[12] In two of these patients, we tested at a dilution no greater than 1:10, but 90% of 'normal' individuals are said to 'respond' to skin testing with rocuronium at this concentration (personal communication, Professor J. Levy). This may throw some doubt on the diagnosis in our patients, but all subsequently received anaesthesia without rocuronium in the same clinical setting without adverse effects. In two patients, the only difference in the anaesthetic technique was in the choice of neuromuscular blocking drug.

Based on the number of vials ordered from the hospital pharmacy, it is estimated that 8800 patients have received rocuronium in our hospital in the past 2 yr, giving an incidence of reaction to this drug of approximately 1:3000. In the same time period, no such reaction to any other neuromuscular blocking agent has been recognized. We are aware of only one other published case,[5] but the Medicines Control Agency (personal communication) has been notified of eight and we are aware of another similar case in an associated hospital (personal communication, Dr E. Ritchie). We suggest that the frequency of reaction to this drug requires close monitoring.

References

1 Hunter JM. Rocuronium: the newest aminosteroid neuromuscular blocking drug. *Br J Anaesth* 1996; **76**: 481–3

2 Puhringer FK, Khuenl-Brady KS, Koller J, Mitterschiffthaler G. Evaluation of the endotracheal intubating conditions of rocuronium (Org 9426) and succinylcholine in outpatient surgery. *Anesth Analg* 1992; **75**: 588–92

3 Cooper R, Mirakhur RK, Clarke RSJ, Boules Z. Comparison of intubating conditions after administration of Org 9426 (rocuronium) and suxamethonium. *Br J Anaesth* 1992; **69**: 269–73

4 Naguib M, Samarkandi AH, Bakhamees HS, Magboul MA, el-Bakry AK. Histamine release and haemodynamic changes produced by rocuronium, vecuronium, mivacurium, atracurium and tubocurarine. *Br J Anaesth* 1995; **75**: 588–92

5 Yee R, Fernandez JA. Anaphylactic reaction to rocuronium bromide. *Anaesth Intensive Care* 1996; **24**: 601–4

6 Fisher M. Treatment of acute anaphylaxis. *BMJ* 1995; **311**: 731–3

7 McKinnon RP, Wildsmith JAW. Histaminoid reactions in anaesthesia. *Br J Anaesth* 1995; **74**: 217–28

8 Watkins J. Second report from an anaesthetic reactions advisory service. *Anaesthesia* 1989; **44**: 157–9

9 Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. *Eur J Anaesthesiol* 1994; **11**: 263–84

10 Laxenaire MC, Moneret-Vautin DA, Geuant JL, *et al.* Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multi-centre epidemiological enquiry. *Ann Fr Anesth Reanim* 1993; **12**: 91–6

11 Laxenaire MC, Gastin I, Moneret-Vautin DA, Widmer S, Geuant JL. Cross reactivity of rocuronium with other neuromuscular blocking agents. *Eur J Anaesthesiol Suppl* 1995; **11**. 55–64

12 *Suspected Anaphylactic Reactions Associated with Anaesthesia.* London: Association of Anaesthetists of Great Britain and Ireland and the British Society of Allergy and Clinical Immunology, 1995

British Journal of Anaesthesia 84 (1): 112–14 (2000)

Fatal paradoxical air embolism during liver transplantation

L. Olmedilla*, I. Garutti, J. Pérez-Peña, J. Sanz, E. Teigell and M. Avellanal

Department of Anaesthesiology, Hospital General Universitario Gregorio Marañón, C. Dr Esquerdo, 46, LE-28007 Madrid, Spain

**Corresponding author*

We describe a case of fatal paradoxical coronary air embolism during liver transplantation. The literature on the diagnosis and prophylaxis of paradoxical air embolism during liver transplantation is reviewed and discussed.

Br J Anaesth 2000; **84**: 112–14

Keywords: liver, transplantation; embolism, air; heart, ischaemia

Accepted for publication: June 17, 1999

Air embolism associated with orthotopic liver transplantation is a well known phenomenon which occurs during the dissection phase while performing vascular anastomosis (inferior vena cava, portal vein) or during liver reperfusion (insufficient hepatic wash out, leaks in vascular anastomoses). A specific problem is the possibility of passage of air bubbles from the right heart to the systemic circulation. Such a paradoxical air embolism can result in air being embolized to the terminal arterial bed of the brain or heart with severe consequences. We present a case of fatal paradoxical air embolism with coronary ischaemia during orthotopic liver transplantation. As far as we are aware, there are no previous reports of paradoxical coronary air embolism during this procedure.

Case report

A 26-yr-old woman with sclerosing cholangitis was admitted for orthotopic liver transplantation. There was no clinical evidence of cardiopulmonary disease in her clinical history or on physical examination. Arterial blood-gas values, chest x-ray, ECG, spirometry and transthoracic echocardiogram were normal. Anaesthesia was maintained with isoflurane in an air–oxygen mixture, with fentanyl, diazepam and pancuronium. Operative monitoring included pulse oximetry, end-tidal carbon dioxide concentration, radial artery cannulation to monitor arterial pressure and a pulmonary artery catheter.

Hepatic dissection was difficult because of the large size of the liver. Unexpectedly, an accidental tear of the suprahepatic inferior vena cava occurred. We observed an increase in pulmonary artery pressures and a decrease in end-tidal carbon dioxide concentration, heart rate and arterial pressure. The tear was sutured and the haemodynamic state was stabilized using atropine 0.5 mg and epinephrine 0.1 mg. We were not using positive end-expiratory pressure (PEEP). Central venous pressure varied between 6 and 10 mm Hg depending on liver manipulation.

Dissection continued and a few minutes later a second tear of the inferior vena cava occurred, allowing air entrainment: end-tidal carbon dioxide concentration and arterial pressure decreased and pulmonary artery pressures increased. The QRS complex of the ECG widened and ventricular tachycardia and fibrillation ensued. Resuscitation was initiated with epinephrine, 100% oxygen, cardiac defibrillation and closed chest cardiac massage. Air and blood (10 ml) were aspirated from the pulmonary catheter. The surgical bed was filled with saline solution and the inferior vena cava was clamped. The patient did not respond to resuscitation. Ventricular fibrillation alternating with asystole was commenced. Approximately 10 min after the second air embolism, an arterial blood sample showed metabolic acidosis with normal potassium and ionized calcium concentrations. We gave sodium bicarbonate, an infusion of lidocaine and bretylium, norepinephrine, and then hyperventilated the lungs. After 60 min there was no spontaneous cardiac activity and so we decided to stop the resuscitation manoeuvres.

An autopsy showed well formed atrial and ventricular cavities and valves with a patent foramen ovale about 2 cm in diameter, coronary arteries without significant stenosis and local myocardial changes compatible with a recent ischaemic event, mostly in the anterolateral wall of the left ventricle.

Discussion

Embolism during orthotopic liver transplantation has been described, and has often been identified using transoesophageal echocardiography. Ellis and colleagues reported 16 patients who underwent orthotopic liver transplantation and observed echogenic material in the right ventricle of all patients using transoesophageal echocardiography.[1] More-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

over, this material moved into the left heart during reperfusion in 2 cases.[1] Usually there are no clinical repercussions; even when massive embolism occurs, patients have been resuscitated successfully. Starzl and colleagues reported 48 patients who underwent orthotopic liver transplantation and developed neurological complications. Arterial air embolism was confirmed at the postmortem examination in two patients.[2] Neither of these series reported evidence of air in the coronary vessels.

After the second embolism, we were surprised by the sudden appearance of arrhythmias and by the ineffectiveness of treatment. We speculate that the second embolism was bigger than the first, although the surgeons informed us that the tear was smaller and that they had clamped the inferior vena cava quickly. It was difficult to quantify the volume of air because increased pulmonary artery pressures and decreased end-tidal carbon dioxide concentrations were affected by clamping the cava, which reduced venous return. We did not have a transoesophageal echocardiogram, which is a sensitive indicator for measuring the volume of the embolism.

Metabolic alterations can precipitate arrhythmias. Blood samples were analysed 30 min before the first venous air embolism, and 10 and 60 min after the second embolism, and showed normal potassium, ionized calcium and pH values.

A pre-existing cardiac abnormality may have affected the response to the embolism, but we found no preoperative evidence of an abnormal feature in this patient (from clinical history, ECG, transthoracic echocardiogram or chest x-ray). There was no evidence of idiopathic ventricular tachycardia (hypertrophy, fibrosis and septal sclerosis) or coronary artery disease at post mortem. Coronary vasospasm has been reported in a young patient during liver transplantation, although it was related to the cold graft being placed close to the right coronary artery.[3]

Therefore, we conclude that a paradoxical air embolism caused coronary obstruction: as little as 0.05 cm^3 of air can cause a focal infarct.[4] Paradoxical air embolism occurs when the air in the venous system or in the right heart passes through some intracardiac channel and reaches the arterial system. It is important to remember that a persisting patent foramen ovale exists in 10–35% of the population, and that the patent foramen ovale is the most common route for paradoxical air embolism.[5] Venous air embolism causes immediate and intense vasospasm in the pulmonary circulation leading to increased right atrial pressure with the potential for flow through a patent foramen ovale.[5] A patent foramen ovale is difficult to detect with transthoracic echocardiography[6] and may not be ruled out even by a contrast transthoracic echo study. A patent foramen ovale was found at postmortem examination in our patient.

Air may also reach the arterial system through pathological dilatation of intrapulmonary vessels normally present in some people (but more frequent in end-stage liver disease).[7] Hopkins, Waggoner and Barzilar found that 47% of patients with chronic liver disease had right-to-left shunting, as determined by contrast echocardiography.[8] Eight of 27 paradoxical coronary embolism cases reviewed by Jungbluth and colleagues[9] were caused by air, but an abnormal intracardiac defect was found in only three. Five air emboli involved the left coronary artery, as in our case, and this is most likely related to its anterocranial position.[9] In the case presented by Ahmat and colleagues, the patient had a coronary air embolism without any intracardiac shunt in the postmortem examination, confirming that patients with liver disease may have less filtering protection against paradoxical air embolism.[10]

An intracardiac and/or intrapulmonary shunt may be detected using contrast transoesophageal echocardiography, but this carries risks in patients with oesophageal varices and does not exclude all those at risk of paradoxical air embolism. [11] When a patent foramen ovale is confirmed in a patient scheduled for posterior cranial fossa surgery, this procedure is better performed with the patient prone rather than seated. However, it is impossible to change either the surgical technique or the patient's position during orthotopic liver transplantation if a patent foramen ovale is discovered. Some authors suggest surgical correction of a patent foramen ovale before posterior fossa surgery[12] but cardiac surgery carries a high risk for patients with end-stage liver disease, and pulmonary shunts may also persist. Transcatheter occlusion of the septal defect may be considered in some cases with a patent foramen ovale.[13]

References

1 Ellis J, Lichtor JL, Feinstein SB, *et al.* Right heart dysfunction, pulmonary embolism, and paradoxical embolization during liver transplantation. A transesophageal two dimensional echocardiographic study. *Anesth Analg* 1989; **68**: 777–82

2 Starzl TE, Scheneck SA, Mazzoni G, *et al.* Acute neurological complications after liver transplantation with particular reference to intraoperative cerebral air embolus *Ann Surg* 1978; **187**· 236–40

3 Ramsay MAE, Takaoka F, Brown MR, Rosenlof P. Coronary artery vasospasm following placement of a cold liver graft during orthotopic liver transplantation. *Anesth Analg* 1989; **69**: 854–5

4 Orebaugh SL. Venous air embolism. *Crit Care Med* 1992; **20**: 1169–77

5 Schwarz G, Fuchs G, Weihs W, Tritthart H, Schalk HV, Kaltenbock F. Sitting position for neurosurgery: experience with preoperative contrast echocardiography in 301 patients. *J Neurosurg Anesth* 1994; **6**: 83–8

6 Cucchiara RF, Nishimura RA, Black S. Failure of preoperative echo testing to prevent paradoxical air embolism. report of two cases. *Anesthesiology* 1989; **71**: 604–7

7 Krowka MJ, Cortese DA. Hepatopulmonary syndrome. Current concepts in diagnostic and therapeutic considerations *Chest* 1994; **105**: 1528–37

8 Hopkins WE, Waggoner AD, Barzilar B. Frequency and significance of intrapulmonary right-to-left shunting in end-stage hepatic disease. *Am J Cardiol* 1992: **70**; 516–19

9 Jungbluth A, Erbel R, Darius H, Rumpelt HJ, Meyer J. Paradoxical coronary embolism: case report and review of the literature. *Am Heart J* 1988; **116**: 879–85

British Journal of Anaesthesia **84 (1)**: 115–17 (2000)

Tension pneumocephalus after neurosurgery in the supine position

G. C. Satapathy and H. H. Dash*

Department of Neuroanaesthesiology, Neurosciences Centre, AIIMS, New Delhi-110029, India

**Corresponding author*

Tension pneumocephalus has been reported most frequently after posterior fossa surgery performed in the sitting position. We present a paediatric patient who developed tension pneumocephalus in the postoperative period after decompression of a craniopharyngioma performed with the patient in the supine position.

Br J Anaesth 2000; **84**: 115–17

Keywords: anaesthesia, neurosurgical; anaesthesia, paediatric; complications, pneumocephalus; position, supine; surgery, neurological

Accepted for publication: August 13, 1999

Pneumocephalus (asymptomatic intracranial air) after craniotomy is a common occurrence.[1 2] The incidence of pneumocephalus after supratentorial craniotomy has been reported to be 100%.[3 4] However, transformation of pneumocephalus into tension pneumocephalus (symptomatic intracranial air) is a rare phenomenon. Tension pneumocephalus after posterior fossa surgery performed in the sitting position has been reported[5–9] but we are not aware of tension pneumocephalus reported after craniotomy in the supine position.

We present the case of a paediatric patient who developed tension pneumocephalus in the early postoperative period after decompression of a craniopharyngioma in the supine position.

Case report

A 10-yr-old, 25-kg boy was admitted with symptoms of headache and vomiting of 1 yr duration. He had bilateral papilloedema but examination was otherwise normal. Haematological and biochemical indices were within normal limits. A CT scan of the head revealed a large mixed density attenuating suprasellar lesion with peripheral calcification and significant hydrocephalus. A diagnosis of craniopharyngioma with gross hydrocephalus was made.

Immediately after admission the child underwent a ventriculoperitoneal shunt under balanced anaesthesia. The intraoperative and postoperative course were uneventful. One week later, he was listed for surgical decompression of the craniopharyngioma to be performed in the supine position. The child was given diazepam 0.2 mg kg^{-1} orally the night before and on the morning of surgery. Glycopyrrolate 0.1 mg and promethazine 0.5 mg kg^{-1} were administered i.m., 1 h before induction of anaesthesia. In the operating theatre, an 18-gauge i.v. cannula was sited on the dorsum of the left hand. Continuous monitoring of the ECG, pulse oximetry and non-invasive arterial pressure was instituted. Thiopental 5 mg kg^{-1} was used for induction of anaesthesia followed by vecuronium 0.2 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with 66% nitrous oxide in oxygen, vecuronium and isoflurane. Pethidine 1 mg kg^{-1} was administered to provide intraoperative analgesia. Invasive arterial pressure (cannulating the left radial artery), central venous pressure (through the right basilic vein) and core temperature (oesophageal temperature probe) were monitored continuously during the intraoperative period. End-tidal carbon dioxide partial pressure was maintained at 3.7–4.0 kPa (Datex AS3). Mannitol 1 g kg^{-1} (125 ml) was infused to provide optimum brain relaxation.

Near total decompression of the craniopharyngioma was carried out with no complications. Surgery lasted 3 h. A total of 1000 ml of crystalloid solutions were given i.v. during the course of the procedure. Residual neuromuscular block was antagonized with neostigmine 50 μg kg^{-1} and atropine 20 μg kg^{-1}. The child's trachea was extubated when he was fully conscious, obeying verbal commands and moving all four limbs. He was transferred to the neurosurgical intensive care unit for postoperative management.

Three hours after surgery, the child's conscious level deteriorated and he became unresponsive. However, he was maintaining his airway and ventilatory frequency was 20 bpm. Oxygen saturation was 97–99% and arterial pressure 110/70 mm Hg. The ventriculoperitoneal shunt was observed to be functioning well. A CT scan revealed a large frontoparietal pneumocephalus without any midline shift (Fig. 1). Frontal twist drill hole aspiration of the pneumocephalus was performed and air gushed out under pressure. Approximately 40 ml of air were drained. The child's sensorium showed

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

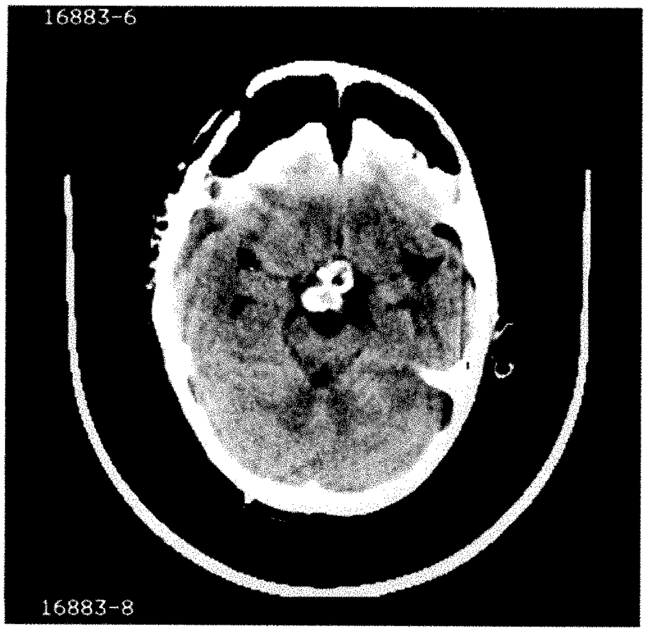


Fig 1 Postoperative CT scan showing a gross frontoparietal pneumocephalus.

marked improvement immediately after frontal drill hole aspiration. He started responding to verbal commands. The remainder of the postoperative course was unremarkable and he was discharged 11 days after operation with no neurological deficits.

Discussion

Postoperative pneumocephalus is commonly observed after intracranial surgery. The amount of intracranial air may vary but it is usually benign in nature and takes approximately 2–3 weeks for complete reabsorption.[4] The presence of pneumocephalus in a patient requiring surgery is of special concern to the anaesthetist because of the possible iatrogenic development of tension pneumocephalus secondary to the use of nitrous oxide,[10 11] as nitrous oxide administration can lead to expansion of any trapped air loculi, thereby increasing intracranial pressure.[12 13] It is likely that patients at highest risk of nitrous oxide-induced tension pneumocephalus are those who have recently undergone a craniotomy and who then must be returned to the operating room for emergency exploration. In these patients it is better to defer the use of nitrous oxide until the dura is opened.

Very rarely, however, a patient may develop tension pneumocephalus immediately after craniotomy or craniectomy. When our patient deteriorated 3 h after surgery we did not consider the possibility of tension pneumocephalus. Emergency CT scan was performed to rule out postoperative intracranial haematoma. But, to our surprise, the scan revealed intracranial air with compression of the frontal horns. This was confirmed further when the intracranial air gushed out under pressure during frontal drill hole aspiration and the child's sensorium improved immediately.

Tension pneumocephalus may present in one of several ways. It may manifest as deterioration of consciousness with or without lateralizing signs,[5–8 11] severe restlessness, generalized convulsions[9] or focal neurological deficit.[6] Cardiac arrest in the immediate postoperative period caused by tension pneumocephalus has been reported in a patient who had undergone posterior fossa surgery in the sitting position.[14]

Several contributing factors have been implicated in the pathogenesis of tension pneumocephalus. They are: (1) nitrous oxide anaesthesia, (2) duration of surgery, (3) gross hydrocephalus, (4) a functional ventriculoperitoneal shunt and (5) intraoperative administration of mannitol.[5 6 11–14] We believe that nitrous oxide played no part in our patient as the child deteriorated 3 h after discontinuation of anaesthesia. Neither was surgery prolonged.

In gross hydrocephalus, a proportionately greater volume of cerebrospinal fluid can be drained during surgery and this can be replaced by air. A functioning ventriculoperitoneal shunt aids in continuous drainage of cerebrospinal fluid from the lateral ventricles into the peritoneal cavity throughout the surgical procedure and in the postoperative period, thereby creating even more space for intracranial air. Our patient presented with gross hydrocephalus because of the craniopharyngioma. His ventriculoperitoneal shunt was also functioning well during the phase of neurological deterioration in the postoperative period.

In retrospect, we believe that administration of mannitol may have enhanced the cerebrospinal fluid loss during the surgical procedure by reducing the brain volume and decreasing the production of cerebrospinal fluid.[15] After completion of surgery, the shrunken brain starts re-expanding to its normal contour after rehydration, normocapnia, brain oedema and replacement of depleted cerebrospinal fluid in the postoperative period.

To prevent accummulation of intracranial air, efforts must be directed to minimize cerebrospinal fluid loss during intracranial surgery. In the presence of gross hydrocephalus with a functioning ventriculoperitoneal shunt, temporary blockage of the shunt may minimize cerebrospinal fluid loss. Cerebral perfusion pressure should be maintained within the normal range by maintaining good hydration. After excision of the tumour, it is better to slowly increase end-tidal carbon dioxide partial pressure towards normal so that the brain can regain its preoperative contour.

Prompt detection of intracranial hypertension caused by tension pneumocephalus[10 13] is aided by intracranial pressure monitoring. The benefits of intracranial pressure monitoring in the immediate postoperative period must be weighed against the associated risks and complications. The major complications of intracranial pressure monitoring are infection,[16] the need to restrict patient movement and monitoring drift or artificially low readings.[17]

In summary, a paediatric patient developed tension pneumocephalus after excision of a craniopharyngioma in the supine position. We believe that this was caused by a combination of contributing factors such as preoperative gross hydrocephalus with functioning ventriculoperitoneal shunt and intraoperative use of mannitol. Prompt diagnosis and immediate management help in salvaging such patients.

References

1 Toung TJK, McPherson RW, Ahn H, Donham RT, Alano J, Long D. Pneumocephalus: Effects of patient position on the incidence and location of aerocele after posterior fossa and upper cervical cord surgery. *Anesth Analg* 1986; **65**: 65–70

2 DiLorenzo N, Caruso R, Floris R, Guerrisi V, Bozzao L, Fortuna A. Pneumocephalus and tension pneumocephalus after posterior fossa surgery in the sitting position: a prospective study. *Acta Neurochir* 1986; **83**: 112–15

3 Domino KB, Hemstad JR, Lam AM, et *al*. Effect of nitrous oxide on intracranial pressure after cranial dural closure in patients undergoing craniotomy. *Anesthesiology* 1992; **77**: 421–5

4 Reasoner DK, Todd MM, Scamman FL, Warner DS. The incidence of pneumocephalus after supratentorial craniotomy. Observations on the disappearance of intracranial air. *Anesthesiology* 1994; **80**: 1008–12

5 Kitahata LM, Katz JD. Tension pneumocephalus after posterior fossa craniotomy, a complication of the sitting position. *Anesthesiology* 1976; **44**: 448–50

6 Lunsford LD, Maroon JC, Sheptak PE, Albin MS. Subdural tension pneumocephalus: report of two cases. *J Neurosurg* 1979; **50**: 525–7

7 Friedman GA, Norfleet EA, Bedford RF. Discontinuation of nitrous oxide does not prevent pneumocephalus. *Anesth Analg* 1981; **60**: 57–8

8 Toung T, Donham RT, Lehner A, Alano J, Campbell J. Tension pneumocephalus after posterior fossa craniotomy: report of four additional cases and review of postoperative pneumocephalus. *Neurosurgery* 1983; **12**: 164–8

9 Dash HH, Bithal PK, Muley S, Vishnoi N, Saini SS, Tandon PN. Tension pneumocephalus following posterior fossa surgery in sitting position. *J Anaesth Clin Pharmacol* 1990; **6**: 207–12

10 Artru AA. Nitrous oxide plays a direct role in the development of tension pneumocephalus intraoperatively. *Anesthesiology* 1982; **57**: 59–61

11 Raggio JF, Fleisher HS, Sung YF, Hoffman JC. Expanding pneumocephalus due to nitrous oxide anesthesia. Case report. *Neurosurgery* **1979**; **4**: 261–3

12 Saidman LJ, Eger EI. Change in cerebrospinal fluid pressure during pneumocephalography under nitrous oxide anesthesia. *Anesthesiology* 1965; **26**: 67–72

13 Skahen S, Shapiro HM, Drummond JC, Todd MM, Zelman V. Nitrous oxide withdrawal reduces intracranial pressure in the presence of pneumocephalus. *Anesthesiology* 1986; **65**: 192–5

14 Thiagarajah S, Frost EAM, Singh T, Shulman K. Cardiac arrest associated with tension pneumocephalus. *Anesthesiology* 1982; **56**: 73–5

15 Sahar A, Tsipstein E. Effects of mannitol and furosemide on the rate of formation of cerebrospinal fluid. *Exp Neurol* 1978; **60**: 584–91

16 Constantini S, Cotev S, Rappaport ZH, Pomeranz S, Shalit MN Intracranial pressure monitoring after elective intracranial surgery. A retrospective study of 514 consecutive patients. *J Neurosurg* 1988; **69**: 540–4

17 Rosenwasser RH, Kleiner LI, Krzeminski JP, Buchheit WA. Intracranial pressure monitoring in the posterior fossa: a preliminary report. *J Neurosurg* 1989; **71**: 503–5

British Journal of Anaesthesia 84 (1) 118–20 (2000)

Severe vasovagal attack during regional anaesthesia for Caesarean section

E. J. Watkins*, M. Dresner and C. E. Calow

Department of Anaesthesia, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

**Corresponding author*

A patient experienced a severe vasovagal attack during regional anaesthesia for elective Caesarean section. The combination of vagal over-activity and sympathetic block produced profound hypotension that threatened the life of the mother and infant. The vasovagal syndrome is described, and its prevention and management discussed.

Br J Anaesth 2000; **84**: 118–20

Keywords: anaesthetic techniques, epidural; anaesthetic techniques, spinal; anaesthesia, obstetric; complications, syncope; complications, vasovagal attack

Accepted for publication: August 31, 1999

Case report

A 29-yr-old woman, parity 1, presented at 38 weeks' gestation for elective Caesarean section because of a high fetal head and a history of previous Caesarean section. Her first pregnancy had ended in an emergency Caesarean section for failure to progress, performed under epidural anaesthesia. Pre-anaesthetic assessment was unremarkable, with no medical problems and a healthy pregnancy. She weighed 70 kg and was 158 cm tall. A combined spinal–epidural, which was our standard technique at the time, was discussed with the patient and consent obtained. Routine antacid premedication was prescribed, consisting of cimetidine 200 mg the night before and the morning of surgery, and 0.3 M of sodium citrate 30 ml in the anaesthetic room.

The patient arrived in the anaesthetic room looking and feeling well, accompanied by her husband. Monitoring of ECG, oxygen saturation and arterial pressure was commenced, showing a heart rate of 90 beat min^{-1} and arterial pressure 133/64 mm Hg. After subcutaneous infiltration of 1% lidocaine, a 16-gauge peripheral line was inserted and a fluid preload of Gelofusine 500 ml was given. With the patient in the sitting position and using an aseptic technique, a total of 4 ml of 1% lidocaine was infiltrated at spinal interspaces L2–3 and L3–4. A lumbar epidural catheter was sited at the L2–3 interspace. After a negative aspiration test, lidocaine 1 mg kg^{-1} was injected into the epidural catheter. During injection of this test dose, the patient complained of feeling dizzy and faint, and became pale. It was noted that she had a heart rate of 60 beat min^{-1} and arterial pressure of 70/35 mm Hg. On direct questioning, the patient denied any symptoms (such as peri-oral numbness, tingling, visual or auditory disturbances or a metallic taste) that would suggest the onset of local anaesthetic toxicity associated with i.v. injection.

A second anaesthetist administered ephedrine 6 mg while the epidural catheter was quickly secured with the intention of lying the patient down. However, with the patient still sitting, the symptoms regressed; heart rate increased to 90 beat min^{-1} and arterial pressure to 90/60 mm Hg. One minute later, arterial pressure was 110/65 mm Hg. There was no sign of a rapidly developing motor block or a high sensory block to suggest subarachnoid catheter placement. A diagnosis of vasovagal attack was made, and it was decided to proceed.

An infusion of ephedrine 30 mg in Gelofusine 500 ml was commenced and spinal anaesthesia performed with a 27-gauge Whitacre needle at the L3–4 interspace, again with the patient in the sitting position. Clear cerebrospinal fluid was obtained and 0.5% hyperbaric bupivacaine 15 mg was injected over approximately 30 s.

Immediately after starting the injection, before one would expect to see cardiovascular changes, the patient once again complained of feeling faint. Infusion of ephedrine was turned to maximum flow, the spinal injection completed, and the patient immediately positioned supine with left lateral tilt. Heart rate was 80 beat min^{-1} but the patient looked pale and grey. Oxygen was administered via a Hudson mask. A second infusion of Gelofusine 500 ml was commenced under pressure and further i.v. bolus doses of ephedrine were given. Ten minutes later, Gelofusine 1500 ml, ephedrine 70 mg and atropine 600 µg had succeeded in producing only brief periods of normotension interspersed with severe hypotension and near syncope. It was decided that prompt

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

delivery of the baby was required for its survival and to remove any contributory aortocaval compression.

The anaesthetic level was T4 to light touch, and Caesarean section proceeded rapidly without complication. A female infant was delivered; she was pale and floppy with a heart rate of 60 beat min^{-1}. Bag and mask resuscitation produced prompt correction of the bradycardia but at 10 min the baby was still floppy and respiratory efforts were laboured. The umbilical cord pH was 6.8. The baby was transferred to the special care baby unit where, over a 2-day admission, she slowly recovered normal muscle tone and respiratory pattern. Postoperative recovery of the patient was unremarkable although she had virtually no memory of the events during the Caesarean section. Three years later, there are no apparent sequelae for mother or baby.

Subsequent careful questioning revealed two relevant episodes in the patient's medical history: one was an unrecorded episode of symptomatic hypotension during the epidural top-up performed immediately before her previous Caesarean section and the other was an episode of profound vasovagal syncope during a hot air balloon ride while several hundred feet above the ground.

Discussion

The differential diagnosis of this haemodynamic collapse includes: i.v. injection of the epidural test dose; high spinal block; or a combination of a vasovagal reflex with spinal-induced sympathectomy. We believe the latter to be the cause because there were no symptoms of local anaesthetic toxicity with the epidural test dose, and the final spinal block was at a level of T4 to touch. The spinal dose of bupivacaine 15 mg was large and is no longer our current practice, but in our view it contributed to the haemodynamic picture rather than being the sole cause.

Vasovagal syncope is a heterogeneous condition. The vagal response can be initiated by external stimuli (e.g. venepuncture or visual input). An alternative mechanism is by stimulation of the Bezold–Jarisch reflex in which low ventricular volumes result in high intraventricular pressures caused by the empty ventricle contracting against itself. This reflex causes parasympathetic activation *and* sympathetic withdrawal resulting in hypotension and bradycardia. The presence of sympathetic withdrawal is supported by the fact that atropine administration may prevent bradycardia but not hypotension.[1] Neurally mediated 'active' vasodilatation may also be involved, as skeletal muscle vasodilatation is greater that that caused by sympathetic withdrawal alone.[1] The Bezold–Jarisch reflex is postulated to be responsible for the condition called 'malignant vasovagal syndrome' or 'neurally mediated syncope' in which patients have recurrent syncope without warning or precipitating stimuli.[2] This condition is often tilt-inducible, and has been labelled 'malignant' because patients can suffer trauma during the sudden unexpected syncopal episodes.[3]

Vasovagal episodes in the anaesthetic room before regional anaesthesia for Caesarean section are not, in our experience, rare. They can occur in either the patient or the partner, and before any procedure has been performed. A vasovagal reaction to venepuncture is common, particularly in the young or in patients with a history of fainting.[4] In this patient, symptoms occurred during placement of the epidural catheter, then appeared to resolve, only to return at the start of subarachnoid injection. The procedure could have been halted at either of these times, but as previous experience indicated that vasovagal activity could be suppressed readily with ephedrine and atropine, it was decided that the best option was to complete the procedure as quickly as possible. In retrospect, this judgement was unwise. The patient may either have suffered a recurrent vasovagal episode or the primary episode may have been prolonged and had only been masked transiently by ephedrine. The outcome was that the combination of vasovagal overactivity and sympathetic block, with aortocaval compression as a likely contributory factor, produced circulatory collapse that was potentially life-threatening to the mother and infant. Just 10 min of this resistant hypotension produced an umbilical cord pH of 6.8 and significant early morbidity in the baby.

How could this woman have been better managed? At the first occurrence of vagal activity, after appropriate treatment with vasoactive drugs, Caesarean section could have been delayed while anticholinergic and sedative premedications were administered. However, anticholinergic premedication may prevent vagally mediated bradycardia, but does not prevent hypotension which is the likely primary event.[5] While there is no rationale to suspect that larger fluid preload might have prevented a vagal reaction, it might have reduced the haemodynamic consequences. Thereafter, a slow onset regional block using the epidural alone or in combination with a much reduced dose of intrathecal local anaesthetic might have been more appropriate. The sitting position should have been abandoned and anaesthesia performed in the operating theatre to facilitate rapid delivery of the baby in the event of haemodynamic collapse. This approach would also be appropriate for an elective case with a history of fainting episodes.

In summary, vasovagal episodes superimposed on regional anaesthesia are a significant hazard. Haemodynamic monitoring and constant vigilance for sudden bradycardia are mandatory during regional anaesthesia, and early and aggressive management of any vasovagal episode is recommended. In the light of this case, it cannot be assumed that anticholinergic drugs alone or in combination with ephedrine will always effectively prevent or treat this problem, and rapid delivery of the infant may be necessary.

References

1 Dietz NM, Joyner MJ, Shepherd JT. Vasovagal syncope and skeletal muscle vasodilatation: the continuing conundrum. *PACE* 1997; **20**: 775–80

2 Hargreaves AD, Muir AL. Lack of variation in venous tone potentiates vasovagal syncope. *Br Heart J* 1992; **67**: 486–90

3 Abi-Samra F, Maloney JD, Fouad-Tarazi FM, Castle LW. The usefulness of head-up tilt testing and hemodynamic investigations in the workup of syncope of unknown origin. *PACE* 1998; **11**: 1202–14

4 Pavlin DJ, Links S, Rapp S, Nessly M, Keyes HJ. Vaso-vagal reactions in an ambulatory surgery centre. *Anesth Analg* 1993; **76**: 931–5

5 Sra JS, Jazayeri MR, Avitall B, *et al.* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia and asystole. *N Engl J Med* 1993; **328**: 1085–90

British Journal of Anaesthesia **84** (1): 121–6 (2000)

BJA

HISTORY

The Woolley and Roe case

J. R. Maltby[1]*, C. D. D. Hutter[2] and K. C. Clayton[3]

[1]*Department of Anesthesia, Foothills Medical Centre, 1403–29th Street NW, Calgary, AB, Canada T2N 2T9.* [2]*Department of Anaesthesia, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK.* [3]*Department of Anaesthesia, Walsgrave Hospital, Clifford Bridge Road, Coventry CV2 2DX, UK*

**Corresponding author*

Albert Woolley and Cecil Roe were healthy, middle-aged men who became paraplegic after spinal anaesthesia for minor surgery at the Chesterfield Royal Hospital in 1947. The spinal anaesthetics were given by the same anaesthetist, Dr Malcolm Graham, using the same drug on the same day at the same hospital. The outcome for the patients and their families was devastating, as it was for the use of spinal anaesthesia in the UK. At the trial 6 yr later, and against the opinion of leading neurologists, the judge accepted Professor Macintosh's suggestion that phenol, in which the ampoules of local anaesthetic had been immersed, had contaminated the local anaesthetic through invisible cracks. In an interview 30 yr after the verdict, Dr Graham believed that the tragedy was caused by contamination of the spinal needles or syringes during the sterilization process. The subsequent explanation that, on the day in question, descaling liquid in the sterilizing pan had not been replaced by water, supported his belief and finally offered a credible explanation. We review the Woolley and Roe case, the status of spinal anaesthesia before and after 1947, and the relevant medico-legal judgments in claims for negligence in the early days of the National Health Service.

Br J Anaesth 2000; **84**: 121–6

Keywords: history, anaesthesia; history, Woolley and Roe; medico-legal; anaesthetic techniques, subarachnoid

Accepted for publication: August 12, 1999

Albert Woolley and Cecil Roe became paraplegic after spinal anaesthesia at the Chesterfield Royal Hospital on Monday, October 13, 1947. Woolley, aged 56 yr, underwent meniscectomy of the knee and Roe, aged 45 yr, had a radical repair of a hydrocoele. The outcome for both men and their families was devastating. It was also devastating for the use of spinal anaesthesia in the UK for the next 25 yr.[1 2] The spinal anaesthetics had been given by the same anaesthetist, Dr Malcolm Graham (1916–1997), on the same day at the same hospital using the same local anaesthetic and the same technique.[3]

We have personal interests in different aspects of the case. Before training in anaesthesia in the Sheffield region in 1967–9, Maltby was in general practice in Chesterfield where he knew Dr Graham. He visited Dr Graham at his home in 1983 and recorded their discussion of the Woolley and Roe case during which Graham revealed unpublished facts and his explanation.[4] Hutter re-examined the case in 1990 and concluded that the most likely cause of the patients' neurological damage was contamination of the syringes and spinal needles by acid descaling solution[5] rather than phenol contamination of the local anaesthetic in the ampoules. Clayton studied legal aspects of the case and interviewed the appeal judge, Lord Denning, during research for his LLM dissertation.[6]

History

The first spinal anaesthetic for surgery in humans was given by Bier in Kiel, Germany, in 1898,[7] using 0.5% cocaine. He soon abandoned the technique because of the toxicity and unpleasant side effects of cocaine. Tropacocaine was introduced in 1895,[8] and stovaine and procaine in 1904.[9] All were less toxic but also less potent than cocaine. Most surgeons, after trying procaine, preferred stovaine or tropacocaine. But side effects and occasional fatalities caused spinal anaesthesia to lose popularity until 1923 when Labat published *Regional Anesthesia*[10] and advocated the use of procaine. He recorded transitory headache, abducens nerve palsy, retention of urine and anal incontinence, but no permanent neurological sequelae after its use.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Fifteen years later in 1936, Brock, Bell and Davison[11] in New York described seven patients who developed a variety of neurological complications after spinal anaesthesia. Two developed aseptic meningitis, one polioencephalitis, one lumbar radiculitis, two cauda equina syndrome and one transverse myelitis. As most patients who received spinal anaesthesia did not develop neurological complications, the authors did not accept a direct chemotoxic effect of the local anaesthetic. The progressive case of cauda equina neuritis led them to suggest that a chemotoxic agent might allow other factors, such as a virus, to operate on neural tissue.

In 1937, Macdonald Critchley, who was an expert witness at the Woolley and Roe trial in 1953, led a discussion on post-spinal neurological syndromes at the Royal Society of Medicine.[12] These included lesions of the cauda equina and conus medullaris with urinary incontinence or retention, and radiculomyelitis with flaccid paraplegia or lower limb weakness. No explanation for this could be offered. During the same meeting, Ferguson[13] reported 13 neurological sequelae of spinal anaesthesia in Manchester in an 18-month period from August 1933 to March 1935 when approximately 1000 heavy duracaine, 1000 stovaine and other spinal anaesthetics had been given. Eight of these patients also had symptoms suggestive of a cauda equina lesion, for which no plausible explanation could be found.

In 1945, Kennedy, Somberg and Goldberg[14] reported three cases of spinal arachnoiditis with paralysis after procaine, eucopaine with procaine, or metycaine spinal anaesthesia. Symptoms commenced 4 days, 21 days and 5 days after operation. Laminectomy in all three patients showed obstructive arachnoiditis. Lysis of the dense adhesions produced modest improvement in two patients. He believed that the evidence for a chemotoxic effect of the anaesthetic drug was ample, and that the technique and infection were rarely to blame. Five years later[15] he described 12 more cases in which symptoms had commenced days to weeks after spinal anaesthesia with a variety of drugs. Most progressed to paraplegia with loss of control of the bowel and bladder. He attributed the neurological damage to the chemotoxic effect of the anaesthetic drug and concluded with an unequivocal condemnation of the technique: 'So, spinal anaesthesia is accompanied by many definite and terrible dangers which are far too little appreciated by surgeons and anesthetists. Paralysis below the waist is too large a price for a patient to pay in order that the surgeon should have a fine relaxed field of operation.'

The true incidence of neurological complications was still unclear when Woolley and Roe received their spinal anaesthetics. Ferguson[13] was one of the few authors who could give the number of spinal anaesthetics from which their cases came. Neurologists mentioned the local anaesthetic drug as the probable cause in most cases, except those of meningitis. They did not discuss methods of sterilization of the ampoules, spinal needles or glass syringes, or the possibility of chemical contamination.

The safety record of spinal anaesthesia was good, considering the lack of routine i.v. fluid loading, re-use of non-autoclaved needles and the fact that surgeons gave their own spinals. According to Dickson Wright, spinals had been used for upper abdominal surgery, and even thoracoplasty, thyroidectomy and craniotomy, without disastrous consequences.[8]

The Woolley and Roe case

Spinal anaesthesia remained popular throughout the 1940s because of the high quality operating conditions it provided. In the late 1940s and early 1950s, its popularity waned as that of general anaesthesia increased. This was because of the introduction of neuromuscular blocking agents,[16 17] training of more anaesthetists who had consultant status in the National Health Service and the widespread publicity associated with the Woolley and Roe trial in the High Court in London in 1953.[3 5 18] The adverse publicity and the uncertainty over the true cause of these tragedies retarded the use of spinal anaesthesia in the UK by 20–25 yr.[1] More than 30 yr after the trial, Macintosh clarified the perceived difference between death from general anaesthesia and paralysis from spinal anaesthesia. In the former, the coroner, on the information available to him, would give his opinion that the unfortunate patient could not stand up to the anaesthetic and would record a verdict of misadventure. In the latter, litigation was likely to follow and result in a large out of court settlement.[17]

The explanation

Hutter re-examined the details of the case in 1990.[5] It is most probable that the fundamental cause of the paralyses was an acidic descaler which, by an oversight, had been allowed to remain in the sterilizing water boiler. The spinal needles and syringes were then boiled in acid which subsequently contaminated the spinal anaesthetic solution when it was withdrawn from the ampoule before injection. This explanation may also account for other earlier unexplained episodes of paralysis after spinal anaesthesia. It appears that the role of the acidic descaler has now been accepted by the anaesthetic community.[1 19]

The evidence before the court

At the trial in 1953, the court accepted Professor Macintosh's evidence that paralysis had been caused by the phenolic sterilizing solution seeping through invisible cracks in the glass ampoules of cinchocaine (percaine, nupercaine).[3] The Court of Appeal upheld this decision in 1954,[5] holding that the anaesthetist could not have been expected to know about this hypothetical risk in 1947. Therefore, because there had been no negligence, Woolley and Roe received no compensation.[3 5]

McNair J said in his judgment: 'In 1947 the general run of competent anaesthetists would not appreciate this risk ...

I accordingly find that by the standard of knowledge to be imputed to competent anaesthetists in 1947, Dr Graham was not negligent in failing to appreciate this risk.'[20] It is clear that this statement has formed the basis of the later Bolam ruling by the same judge[21] that: 'The test is the standard of the ordinary skilled man exercising and professing to have that special skill. A man need not possess the highest expert skill at the risk of being found negligent. It is a well established law that it is sufficient if he exercises the ordinary competent skill of an ordinary competent man exercising that particular art.'

An editorial in the *British Journal of Anaesthesia* at that time[22] considered this sequence of events to be unlikely and thought it more probable that there had been contamination of the spinal cinchocaine with a different chemical irritant. Graham later identified the sterilizing process as the most likely source of contamination. The theatre sister responsible for this had been ill with violent headaches and vomiting on that day, and went off duty at lunchtime. She subsequently underwent successful removal of a pituitary tumour. He considered it plausible that she had failed to supervise the preparation of the needles and syringes.[23 24]

Graham did not believe the 'invisible crack theory' or the role of phenol. In 1983, he recalled that when ampoules were produced in court for his inspection he could eventually find the cracks but commented, 'These are thermal cracks, are they not?' He knew that cracks had been made in Oxford by touching ampoules with a hot wire. He and his colleague in Chesterfield had done 'all sorts of experiments banging them about and we couldn't crack one. We could smash them, but we couldn't crack them... They either broke altogether or nothing happened—unless you put a hot wire on them'.[23 24]

Further to this, and unknown to the court, Graham was aware that a third patient, who was very ill from intestinal obstruction and died a few days later, had probably also suffered neurological sequelae after a spinal anaesthetic on the same day as Woolley and Roe.[5 23 24] This could only have added support to Graham's belief that if three things happen in one day, there's a common cause; something went wrong, probably with the sterilizing procedure, that involved all three spinal anaesthetics on that one day.[24] The court never heard these views of Graham, and ignored the evidence of the neurologists[5 23] that phenol could not have caused these paralyses. Consideration of animal experiments in the physiological laboratory at Oxford to determine the effect of various concentrations of phenol on the spinal cord had been left too late. A letter from Bryce Smith to the plaintiffs' solicitors dated October 8, 1953,[25] 5 weeks before the trial, explained that these could not start for 2–3 weeks and that no definite report could be given for approximately 6 months. In his judgment,[20] McNair J also considered the significance of the severe headache suffered by Roe during and after the spinal injection. He argued that premedication of omnopon gr. 1/3 (20 mg) and scopolamine gr. 1/150 (0.4 mg) would have made Roe's recollection of events during surgery uncertain, and that headaches were not uncommonly associated with spinal anaesthetics. He thus dismissed Roe's intraoperative headache as being of no relevance to the case and appears to have leaned over backwards to discredit Roe's evidence. He ignored the fact that, although post-spinal headaches occur after operation, Roe's had occurred immediately after injection of the local anaesthetic. The *British Journal of Anaesthesia* editorial[22] considered that this headache was not consistent with the phenol theory. On the contrary, it was good evidence for contamination of the spinal anaesthetic with a different chemical irritant. Cope's account of the trial[3] shows that Macintosh contradicted himself on whether there had been earlier episodes of neurological sequelae after spinal anaesthesia similar to the symptoms suffered by Woolley and Roe in which phenol would not have been present. If the court had pursued this point, the phenol theory would have been much more difficult to sustain.

Was acid contamination of syringes and needles foreseeable? Evidence was given at the trial that they were boiled for 20 min and, allegedly, washed in sterile distilled water.[3] This was the delegated responsibility of the theatre sister and her staff. It seems unlikely that Graham was aware that the theatre sister descaled the sterilizer with a strongly acid solution. At the trial it was stated that the solution in which the ampoules were soaked was coloured blue for 1/20 phenol and pink for 1/40 phenol.[3] Graham's statement that the colouring was to identify the solution as phenol[4] and not to detect contamination of the local anaesthetic is confirmed in Macintosh's letter of August 21, 1953 to the plaintiffs' solicitors that the stock solution of phenol from the hospital dispensary was coloured a faint pink to distinguish it from water and other substances in the dispensary.[25] If Graham had been aware of the sister's descaling procedure, it is possible that he would have ordered dye to be added to the descaling liquid to ensure that it was discarded and replaced with colourless water before instruments were placed in the pan to be sterilized.

Vandam and Dripps later reported a prospective study of 10 098 patients who received spinal anaesthetics and were followed-up for 6 months.[26 27] Sixty-six patients developed numbness or tingling in the lower limbs or feet that usually disappeared within 1 yr. Only one patient, who had an unsuspected spinal cord meningioma, developed incapacitating neurological disease. Greene acknowledged this safety record in 1961 in a comprehensive review of neurological complications.[28] He described cases of chronic adhesive arachnoiditis with clinical symptoms similar to those of Woolley and Roe as the most frequently encountered lesion but was unable to ascribe a specific cause. He attributed the overall decrease in neurological sequelae to the lack of histotoxic properties of procaine and amethocaine (tetracaine, pontocaine), strict aseptic technique and avoidance of detergents, germicides and chemicals during cleaning of spinal sets which, including ampoules, must be autoclaved.

McNair J and Lord Denning: their contributions to the development of medical law

Lord Denning was sitting in the Court of Appeal in 1951 when the case of a plaintiff, whose hand had been left useless after elective surgery, came to appeal in *Cassidy v Ministry of Health*.[29] This presented an opportunity for final clarification of hospital liability. The trial judge had found in favour of the hospital because the plaintiff had not proved negligence against any of the hospital staff. However, the Court of Appeal overturned the verdict, applying the doctrine of *res ipsa loquitur* because the hospital had failed to rebut the negligence claim. Denning made the point that, when a hospital accepts a patient for treatment, it provides that treatment through the staff that it employs. If the staff are negligent in giving the treatment, the hospital is just as liable as anyone else who employs others to perform duties on their behalf.

The National Health Service had come into being in 1948. This opened the door to a radical change in judicial policy towards the rights of patients and Denning's judgment pointed the way. The Cassidy case in 1951 was a turning point in the evolution of the theoretical basis of the master and servant relationship at common law. Denning pointed out that the cause of the fallacy in the reasoning of the Hillyer case in 1909[30] was the anxiety to protect voluntary hospitals from economic disaster if they were held responsible for the errors of their staff. After the verdict, the *British Medical Journal*[31] took Denning to task because it thought the fallacy was being corrected at the expense of a local authority.

In 1952, Professor Aird[32] highlighted the unilateral character of medico–legal battles. Consultants were hesitant to offer expert evidence for a plaintiff, however deserving, or for a hospital governing body, however harassed. When Macintosh had misgivings about going into the witness box in the Woolley and Roe case, Roe's solicitors wrote him a letter dated January 14, 1953, that stated, in part: 'May I remind you how I put my troubles before you when we first met at luncheon with Dr Geikie Cobb? I gave you the history of the attempts made by the plaintiff's solicitors in the north and later by me in London, to enlist the assistance of an anaesthetist of standing... I told you how one after another the consultant anaesthetists who were approached, after indicating sympathy with the plaintiffs and sometimes condemnation of the defendants, flatly refused to give evidence against a fellow practitioner. I think I gave you a copy of the memorandum I had then in desperation drafted for the medical journals and the GMC, contending that the interests of justice would be seriously compromised unless a responsible authority on this branch of medicine would consent to advise and give evidence for the plaintiffs. I believe that when you consult your files you will find clear evidence that it is your evidence that we have always relied on getting.'[25] Macintosh replied that his views had not changed and he agreed that evidence should be given against an anaesthetist who has been obviously careless or negligent.[25]

Later, in 1953, Denning conveyed some of his worries that had been created by Cassidy in his book *The Changing Law*.[33] He wrote that, 'In the days before nationalisation, the law was very tender towards the charitable hospitals.... That decision [Cassidy] has had widespread repercussions. Before nationalisation a case against a hospital was a rare thing. Now it is a very common thing. I do not suppose there is more negligence than there was before. The difference is that there is now a recognised legal remedy against the nationalised service. Not every point has however been cleared up.' It appears that from this point it became Denning's holy grail to protect doctors who felt vulnerable to charges of negligence by his own judgment in Cassidy.

In a case heard in May 1953,[34] a patient's left arm had become paralysed after operation and he was awarded £4000 as damages. Denning demonstrated his changed attitude to the medical profession. The arm had been abducted at 80° during surgery for a blood transfusion. Six months before the incident, an article in the *Lancet*[35] had warned against this risk. The trial judge took the view that failure to keep abreast of the professional journals was negligence. However, in the Court of Appeal, Denning overturned the judgment on the grounds that, if negligence amounted to no more than this, it was not enough. He concluded that it would be putting too high a burden on the medical man to say that he must read every article in the medical press.[36]

In the Woolley and Roe case in 1954,[37] Denning restated that hospital authorities are responsible for the whole of their staff, not only for the nurses and doctors, but also for the anaesthetist and surgeon. The only exception was the case of surgeons or anaesthetists selected and employed by a private patient. Regarding negligence, he stated that each of these plaintiffs, Woolley and Roe, was entitled to say to the hospital: 'While I was in your hands something has been done to me which has wrecked my life. Please explain how it has come to pass.' The hospital had explained that there were invisible cracks in the ampoules. When the ampoules were immersed in phenol to sterilize them, phenol had contaminated the local anaesthetic. This resulted in paralysis of the patients.

Denning used Goodhart's 1926 article[38] to argue that the person who is guilty of causing injury or damage should only be held liable for what a reasonable man in his position would have avoided by due care. The idea was to introduce foreseeability in place of probability. Denning argued that the test of duty depended on what you should foresee. The next question was whether the neglect of duty was a 'cause' of the injury. The chain of causation was broken when an intervening action occurred that you could not reasonably be expected to foresee. Only when those two preliminary questions, duty and causation, were answered in favour of the plaintiff did the third question, remoteness of damage, come into play. Denning thought that, in the case of a crack in an ampoule that was invisible to the naked eye, the only foreseeable consequence was loss of local anaesthetic, not paralysis of the patient. The hospital authorities were therefore not liable. He concluded, 'One final word. These two men have suffered such terrible consequences that there is a natural feeling that they should be compensated. We must insist on due care for the patient at every point, but we must not condemn as negligence that which is only misadventure.'

Variations of this last sentence appeared in several of Lord Denning's later judgments on medical negligence. A reluctance to find against doctors in negligence cases became a Denning characteristic. In his 1979 book, *The Discipline of Law*,[39] he revealed the reasoning behind his change from pro-patient in *Cassidy v Ministry of Health* (1951) to pro-doctor in *Woolley and Roe v Ministry of Health and Others* (1954) and subsequent cases. Denning wrote: 'As a result of that case [Cassidy], the medical profession became alarmed. It seemed to have opened the door to many groundless charges of negligence. This became known to us—from articles in journals and periodicals and so forth. The courts are, I find, always sensitive to criticism. So in the next case [Woolley and Roe], we sought to relieve the anxieties of the medical men.'

This statement has been analysed and reviewed. One writer hypothesized that, 'presumably 'so forth' refers to innumerable encounters between judges and the higher ranks of the medical profession in their clubs.'[40] Also, the Cassidy case had been heard in the last 2 months of the Attlee government and Roe during Churchill's. Was political pressure applied to protect the National Health Service from increasing negligence charges? When asked about these possibilities by one of the authors (K. C. C.), Lord Denning said that lawyers and medical men rarely met in their clubs and categorically denied any political interference. His own explanation was more simple. The only influence was that of McNair J, who heard the original case and found no negligence. As an afterthought, Denning pointed out that McNair's sister was a doctor.

Many doctors felt at the time that Woolley and Roe should have received compensation, but not at the expense of a colleague's reputation. In 1955, a year after the appeal, Denning wrote that there was no way of giving compensation as the law stood.[41] The law would have to adopt a new test, asking who should pay rather than whose fault it was, with hospital authorities carrying appropriate insurance. Perhaps he had in mind something similar to present day no blame insurance in New Zealand. Against this was the argument that any person, employer or doctor who is negligent should be reprimanded, but should not suffer reprimand if innocent. He believed that if you make compensation payable without proof of negligence, you remove the moral basis of law. McNair and Denning shaped medico-legal case law in the 1950s, leaving a legacy that was successfully built upon over subsequent decades.

Biographical notes

John McNair, Justice [William] McNair's father, was a Lloyd's broker who had three children (William, Arthur and Dorothy). Arthur became a consultant in obstetrics and gynaecology, and vice president of the Royal College of Obstetricians and Gynaecologists. William (1892–1979) became a distinguished lawyer and received a knighthood in 1946 for services as legal advisor to the Ministry of War Transport during the Second World War. He sat on the Queen's Bench from 1950 to 1966. As well as hearing the Roe case in the High Court, he made the definitive judgment in the case of *Bolam v Friern Hospital Management Committee* (1957),[21] a landmark case. Dorothy trained as a doctor at the Royal Free Hospital and went into general practice at Dulwich, holding anaesthetic appointments at the South London and at Sydenham Children's Hospitals throughout the Second World War. With the introduction of the NHS, she devoted herself entirely to anaesthesia and was elected FFARCS in 1951. A former colleague, Dame Josephine Barnes, recalls Dorothy as a most competent anaesthetist with superb organizational ability, one of the subjects of the latter skill being her younger brother William! Neither William nor Dorothy married and they shared the family house in Dulwich. They mixed in the same circle of friends and shared the same passion for fishing, along with their brother Arthur. If there were medical anxieties, they would almost certainly have been discussed, at least informally. William, Arthur and Dorothy McNair have all died.

Denning (1899–1999) was called to the bar in 1923, became a KC in 1938, and a judge of the High Court of Justice in 1944. He was knighted in 1944 and created a life peer in 1957. In 1962 he was appointed Master of the Rolls. He died on March 5, 1999, 6 weeks after his 100th birthday, leaving a legacy few will match.

References

1 Morgan M. The Woolley and Roe Case. *Anaesthesia* 1995; **50**: 162
2 Wildsmith JAW. Spinal anaesthesia—the second fifty years. *History Anaesth Soc Proc* 1998; **23**. 40–2
3 Cope RW. The Woolley and Roe case. Woolley and Roe versus Ministry of Health and others. *Anaesthesia* 1954; **9**: 249–70
4 Graham JM, Maltby JR. *The Woolley and Roe Case* (audiotape discussion and transcript). Archives, Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1 3RA, UK
5 Hutter CDD. The Woolley and Roe Case. A reassessment. *Anaesthesia* 1990; **45**: 859–64
6 Clayton KC. *Lord Denning—His Contribution to Medico-Legal Jurisprudence*. Dissertation. Cardiff: University of Wales, 1995; 61
7 Bier A. Versuche über Cocainiserung des Ruckenmarkes. *Z Chirurg* 1899; **51**: 361–9
8 Wright AD. Spinal analgesia with special reference to operations above the diaphragm. *Proc R Soc Med* 1931; **24**: 613–20
9 Lee JA. *A Synopsis of Anaesthesia*, 2nd Edn. Bristol: John Wright and Sons, 1950; 165
10 Labat G. *Regional Anesthesia*. Philadelphia: WB Saunders, 1923; 436–55

11 Brock S, Bell A, Davison C. Nervous complications following spinal anesthesia· A clinical study of seven cases, with tissue study in one instance. *JAMA* 1936; **106**: 441–7

12 Critchley M. Discussion on the neurological sequelae of spinal anaesthesia. *Proc R Soc Med* 1937; **30**: 1007–32

13 Ferguson FR. Discussion on the neurological sequelae of spinal anaesthesia. *Proc R Soc Med* 1937; **30**: 1020–4

14 Kennedy F, Somberg M, Goldberg BR. Arachnoiditis and paralysis following spinal anesthesia. *JAMA* 1945; **129**. 664–7

15 Kennedy F, Effron AS, Perry G. The grave spinal cord paralyses caused by spinal anesthesia. *Surg Gynecol Obstet* 1950; **91**: 385–98

16 Hughes R. Neuromuscular blocking agents. In: Atkinson R S, Boulton T B, eds. *The History of Anaesthesia*. London: Parthenon Publishing Group, 1989; 257–67

17 Macintosh RR. Lest we forget: spinal analgesia. *Anaesthesia* 1975; **30**: 479–83

18 Hutter CDD. The Woolley and Roe Case—II: An explanation In: Schulte am Esch J, Goerig M, eds. *The Fourth International Symposium on the History of Anaesthesia*. Lubeck: DragerDruck GmbH, 1997; 219–21

19 Atkinson RS, Rushman GB, Davies WJH *A Synopsis of Anaesthesia*, 11th Edn. Oxford: Butterworth-Heinemann, 1994; 693

20 Royal Courts of Justice, Thursday, November 12, 1953. Cecil Henry Roe v Ministry of Health, Dr J Malcolm Graham, and Ciba Laboratories. Albert Woolley v Ministry of Health and Others. Judgment (transcript of shorthand notes of the Association of Official Shorthandwriters, Ltd, Room 392, Royal Courts of Justice, and 2, New Square, Lincoln's Inn, London WC2)

21 Bolam v Friern Hospital Management Committee (1957). I WLR 582

22 Editorial. *Br J Anaesth* 1954; **26**: 233–6

23 Maltby JR. The Woolley and Roe Case. *Anaesthesia* 1991; **46**: 426

24 Maltby JR. The Woolley and Roe Case—I: The anaesthetist's thoughts. In: Schulte am Esch J, Goerig M, eds. *The Fourth International Symposium on the History of Anaesthesia*. Lubeck: DragerDruck GmbH, 1997; 213–8

25 Macintosh papers, file PP/RRM/A.62. Contemporary Archives Medical Centre, the Wellcome Institute for the History of Medicine, 183 Euston Road, London NW1 2BE

26 Vandam LD, Dripps RD. A long term follow-up of 10,098 spinal anesthetics II: incidence and analysis of minor sensory neurological defects. *Surgery* 1955; **38**: 463–9

27 Vandam LD, Dripps RD. Long term follow-up of patients who received 10,098 spinal anaesthetics: neurological disease incident to traumatic lumbar puncture during spinal anaesthesia. *JAMA* 1960; **172**: 1483–7

28 Greene NM. Neurological sequelae of spinal anesthesia. *Anesthesiology* 1961; **22**: 682–98

29 Cassidy v Ministry of Health. 1951; 1 All ER, 574

30 Hillyer v St Bartholomew's Hospital. 1909; 2KB 820

31 Medico-legal. Responsibility of hospital management. *BMJ* 1951; **1**: 480

32 Aird I. Letters—Negligence. *The Times*. 1952; May 23: 7 (col 5)

33 Denning AT. *The Changing Law*. London: Stevens, 1953; 30

34 Medicine and law. Successful appeal against verdict of negligence *Lancet* 1953; **265–2**: 1320

35 Ewing MR. Postoperative paralysis in the upper extremity. *Lancet* 1950; **258–1**: 99–103

36 Medico-legal. Anaesthetist not negligent. *BMJ* 1953; **2**: 1329

37 Roe v Ministry of Health. 1954; 2 All ER, 131

38 Liability for the consequences of a negligent act. AL Goodhart Cambridge Legal Essays, 1926; 101–21

39 Denning AT. *The Discipline of Law*. London: Butterworths, 1979; 241

40 Jowell JL, McAuslan JPWB. *Lord Denning: The Judge and the Law*. London: Sweet and Maxwell, 1984; 318

41 Denning AT. *The Road to Justice*. London: Stevens, 1955; 116

British Journal of Anaesthesia **84** (1): 127–8 (2000)

Correspondence

Putting the sterile syringe packaging to good use

Editor—Occasionally, there is a need to repeatedly syringe blood or other fluid into the patient for volume resuscitation. An objection that some clinicians have to this practice is that the shaft of the syringe plunger may come into contact with the physician's hand as they draw fluid into the syringe. If any portion of the plunger then comes into contact with the inside of the syringe, the next volume of fluid that is drawn into the syringe may become contaminated. The plunger is not designed to come into contact with the inside of the syringe casing, otherwise friction will occur when the plunger is withdrawn or pushed in.

This concern of contamination of the plunger can be eliminated by the following method. The plastic sterile packaging of the 2- or 5-ml syringe should be cut or torn neatly at the end opposite to the plunger. The syringe is then pushed out from this end of the pack. Without removing the plastic packing completely, it now forms a sterile sheath protecting the plunger as it is withdrawn to fill fluid (Fig. 1). The opened end of the packing can be fastened to the syringe casing with adhesive tape or a rubber-band. The plastic pack can now be handled by the clinician without the risk of contamination during syringing. This practice is cheap and safe. It makes use of everything that the syringe manufacturer has to offer.

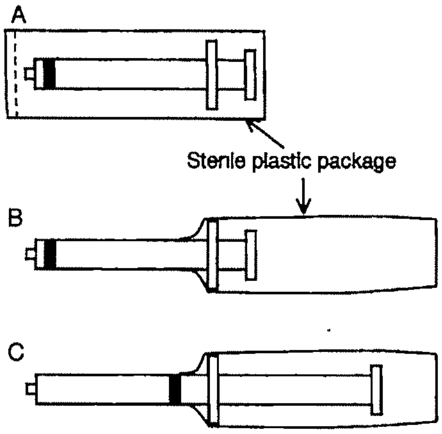


Fig 1 A: Sterile syringe in the sterile plastic package with a dotted line intended to cut or tear B: The intended position of the plastic packing; the opened end can be fastened to the syringe casing with adhesive tape or a rubber band. C. The plunger withdrawn to the full extent. At no time is the plunger in contact with the hand.

Commercially, syringe manufacturers should think of re-designing the packaging of large capacity syringes to facilitate this practice. An ideal plastic packaging could incorporate the following characteristics: a demarcation strip at the end of the packaging; the strip should be of a certain width to allow easy tearing; and the material of the plastic pack should be able to withstand repeated crumpling during re-syringing. The packaging should also be loose-fitting to allow the syringe to be pushed through it easily. It should have a clear surface without markings to allow calibrations of the syringe to be seen.

N. C. Hwang
Y. W. Chan
Department of Anaesthesia
Singapore General Hospital
Singapore

Identifying tracheomalacia

Editor—Tracheomalacia after thyroidectomy is a well-known, although uncommon, condition and its identification is essential to prevent life-threatening airway obstruction after operation. Clinical assessment of tracheomalacia before tracheal extubation may be done by direct palpation of the trachea. In addition, obstruction to passage of a suction catheter beyond the tip of the tracheal tube as it is withdrawn gradually in a spontaneously breathing patient would suggest tracheal collapse. Fibreoptic bronchoscopy and pulmonary flow–volume loop studies have been used to confirm the presence of tracheomalacia.[1]

We describe a simple and economical method to detect tracheomalacia which can be performed on the operating table at the end of surgery. To ensure atraumatic tracheal intubation, the tracheal tube used is one size smaller than the ideal. The range of sizes inserted in our patients was 7.0–8.5 mm. The cuff of the tracheal tube is placed below the rima glottidis but above the carina. Peritubal leak and airway pressures before cuff inflation are noted The minimum volume of air in the cuff needed to produce an airtight seal in our series was 10.5 ± 2.5 ml. At the end of surgery, before antagonism of residual neuromuscular block, the cuff of the tracheal tube is deflated after thorough suctioning of the oropharynx. Tracheomalacia would result in tracheal collapse over the tube preventing peritubal leak after cuff deflation. The presence of a leak would exclude tracheal collapse. Any decrease in the volume of air needed in the cuff to make an airtight seal would also indicate tracheomalacia. In two of our patients, this volume decreased to 4.5 ± 1.5 ml.

This method was applied in 80 patients undergoing thyroidectomy during the period January 1997 to April 1998. The male:female ratio was 33:47, mean age was 48.7 (range 26–74) yr, and body weight was 41–79 kg (mean 55.0 ± 12.9 kg). The mean weight of excised thyroid mass was 306.3 ± 244.6 g (range 80–700 g). All patients had either grade II or III thyromegaly.[2] Duration of thyroid enlargement was 4–38 yr. The surgical procedures lasted 3 8 ± 1.4 h.

None of the patients had signs of recurrent laryngeal nerve palsy after operation. Careful examination of the vocal cords did not reveal glottic or sub-glottic oedema, nor was there any haematoma in the immediate postoperative period in any patient. However, six of the 80 patients, including one who developed tracheomalacia, had features suggestive of hypocalcaemia in the immediate postoperative period.

The test detected tracheomalacia in two patients, and this was confirmed later by pulmonary flow–volume loop studies. There were no false negative results. Although immediate tracheal collapse can be detected using this technique, patients may still develop tracheomalacia up to 24 h after operation.[3]

P K Sinha
P. K. Dubey
S Singh
Department of Anaesthesiology and Critical Care Medicine
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Lucknow, India

1 Geelhoed GW. Tracheomalacia from compression goiter management after thyroidectomy. *Surgery* 1988; **104**: 1100–8
2 Perez C, Scrimshaw NS, Munoz AJ. Technique of endemic goiter

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

surveys. In: *Endemic Goiter*. Geneva: World Health Organization, 1960: 369

3 Cooke RV. Thyroid disease and thyroidectomy. *Ann R Coll Surg Engl* 1966; **39**: 201–12

Haemodynamic and/or tonometric monitoring in cardiac surgery

Editor—If shock is defined as a systemic stage of oxygen supply-dependency, most sensitively established from the gastric intramucosal acidosis caused by the net accumulation of protons in anaerobiosis and most specifically excluded by the presence of a normal gastric intramucosal pH, then the following statements may be made about Bams, Mariani and Groeneveld's[1] recent ICU study of 'haemodynamically compromised' patients who had cardiac surgery.

Despite being 'haemodynamically compromised', two-thirds of the patients were not in shock on admission to the ICU or 12 h after admission. 'Haemodynamic compromise' was not a sensitive, specific or accurate indication of the presence or absence of shock and hence of the appropriateness, success or failure of the resuscitative efforts administered either during or after surgery. Nine (19%) patients who were not in shock on admission developed shock in the next 12 h and 10 (45%) who had been in shock were still in shock 12 h later. Therefore, the resuscitative efforts administered in the first 12 h in the ICU, which were directed by global haemodynamics, were often ineffective in shocked patients or caused shock in adequately resuscitated patients. Gastric intramucosal pH reflected appropriately the absence of any net change in mortality risk achieved by 12 h of haemodynamically directed management, as documented by admission and 24-h measurements in other studies of IC patients, but the differences did not achieve statistical significance. Measurements should have been made during surgery and more frequently to fully demonstrate their predictive value as we and others have reported.[2 3]

The specifics of these statements would change if the cut-off between normal and abnormal measurements, most appropriately determined from the statistical limits of normality. were different, but the point of the statements would not. Having a sensitive and specific measure of the presence or absence and degree of systemic oxygen supply-dependency has the potential to alter the logic of patient management and improve the precision, efficacy and cost-effectiveness of care by avoiding unnecessary, ineffective and harmful interventions and promoting the evolution of increasingly effective management practices.

Measurements of intramucosal $P\text{CO}_2$ or less conveniently but more accurately $P\text{CO}_2$ gap, provide very specific means of detecting acute regional perfusion failure but normal measurements do not exclude the presence of an intramucosal acidosis caused by impairment of oxygen uptake or 'cytopathic hypoxia'. Haemodynamic measurements add value in so far as they help to define the severity of the shock present in patients with an intramucosal acidosis and the risk of developing myocardial as opposed to other organ dysfunction and failure, but can be very misleading if used without the support of tonometric measurements to direct management.

R. G. Fiddian-Green
Constantia
Western Cape
South Africa

1 Bams JL, Mariani MA, Groeneveld ABJ. Predicting outcome after cardiac surgery: comparison of global haemodynamic and tonometric variables. *Br J Anaesth* 1999; **82**: 33–7

2 Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: comparison with other monitoring. *Crit Care Med* 1987; **15**: 153–6

3 Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Med* 1994; **20**. 99–104

Editor—We thank Dr Fiddian-Green for his comments. Although we do not understand all of the points, we would like to clarify some of the issues he raised.

Inclusion of patients was not based on 'shock' but on the presence of hypotension (<75 mm Hg) and the need for a relatively high dose of dopamine (i e. $>8\ \mu\text{g kg}^{-1}\ \text{min}^{-1}$) in the intensive care unit. The reason for these inclusion criteria is that shock is difficult to define. Dr Fiddian-Green erroneously equates a low pH with 'shock'. A high or increasing $P\text{CO}_2$ gradient (e.g. a low or decreasing pHi) measured in the stomach lumen during support of global haemodynamics was associated with a slight increase in mortality risk. A type II error can indeed cause this increase (which was not statistically significant).

Obviously, we may have missed a difference in $P\text{CO}_2$ gradient between outcome groups, which might have become apparent if more serial measurements had been performed in the disease course until death in the ICU or discharge. This does not invalidate our conclusion that, in a relatively large group of post-cardiac surgery patients with an increased risk of haemodynamic abnormalities and mortality, early global haemodynamic variables were of better predictive value for ICU mortality than regional (e.g. tonometric) variables, in spite of treatment being guided by global rather than tonometric variables. Tonometric variables did not have independent and additive predictive value, beyond the systemic haemodynamic abnormalities. Therefore, we cannot exclude the fact that hypotension, relatively unresponsive to treatment and predictive of a poor outcome, was not accompanied, in many of these patients, by global or gastric mucosal hypoperfusion, at least shortly after surgery. Conversely, our results do not support the suggestion of Dr Fiddian-Green that treatment guided by systemic haemodynamics worsens outcome. The proposition that early treatment of haemodynamically compromised patients after cardiac surgery should be guided by tonometric rather than by systemic haemodynamic variables and that this improves outcome was not supported by our study.

Furthermore, there is no consensus to treat patients who are haemodynamically compromised on the basis of tonometric variables rather than on routinely obtained, and normally accepted, haemodynamic variables. However, we cannot exclude a better outcome if treatment decisions had been based on both global and regional variables. This would be difficult to achieve in the absence of a uniformly accepted strategy to decrease an elevated gastric mucosal to blood $P\text{CO}_2$ gradient.

J L. Bams
Department of Cardiopulmonary Surgery
University Hospital Groningen
Groningen, The Netherlands

A. B. J. Groeneveld
Medical Intensive Care Unit
Free University Hospital
Amsterdam, The Netherlands

British Journal of Anaesthesia 84 (1): 129–30 (2000)

Book Reviews

What A Blessing She Had Chloroform. The Medical and Social Response to the Pain of Childbirth from 1800 to the Present. D. Caton. Published by Yale University Press. Pp. 288; indexed. Price £20.00.

We had been discussing an audit of our obstetric epidural practice at a departmental meeting when one of my colleagues remarked that he could not understand all the fuss because his wife had never needed anything other than a few puffs of Entonox for any of her deliveries. By way of contrast, one of our trainees had an epidural in labour and afterwards remarked that it was one of the best things that had ever been done for her. Another woman I know hated the loss of feeling resulting from the epidural she had received for her first delivery. That was in the days before low-dose epidural analgesia had been discovered. She much preferred the Entonox she used for her second delivery because it allowed her to retain control.

These anecdotes only serve to remind anaesthetists of the variability of the response shown by women to the pain of labour. They are echoed in Donald Caton's book, *What a Blessing She Had Chloroform*, and sub-titled *The Medical and Social Response to the Pain of Childbirth from 1800 to the Present*, where in the final chapter he recounts his overhearing two obstetric nurses talking. One declares that in her next pregnancy she wants an epidural inserted at 7 months. The other admits that while giving birth to her two children without any anaesthesia was hard, she thought that the experience made her a better person. Caton had worked with both nurses and notes that there was a noticeable difference in the way they handled their patients and in the frequency with which they requested epidural analgesia for women in their care.

The book represents his attempt to understand and explain the reactions of women to the pain of childbirth. It is based in part on the author's articles published in *Anesthesiology* between 1970 and 1996 and is divided into three sections. These deal in turn with the history of the medical management of the pain of childbirth, the social reactions to childbirth, and the interaction between medical practice and social values. The sub-title aptly describes the subject matter. It is not a conventional account of the history of anaesthesia, nor is it a book dealing with the medical and social responses to pain separately. The author attempts to put the medical response to obstetric pain into a social context. I think that he largely succeeds. The first section is the easiest to read as it is a relatively straightforward account of the history of anaesthesia during the 19th century, albeit with an emphasis on obstetrics. Most of the originators of our specialty make an appearance. The names Snow, Morton, Clover, Simpson, Bigelow and Wendell Holmes will be familiar to most anaesthetists, while those of Meigs, Channing, Keep and others will not. The tremendous cross-fertilization of ideas between the USA and the UK is made apparent, as also is the antipathy between some of the early protagonists.

The middle section is the longest and most complicated, while the final section is quite short. The views of opinion formers changed enormously in the years between 1844, when Crawford Long successfully used ether to anaesthetize a patient, and 1944 when Grantly Dick Read published the first American edition of his book on natural childbirth. The latter was in part a reaction to the increasing use of drugs to obliterate the pain of labour, a process culminating in the advocacy of the ill-fated Twilight Sleep Association. The contribution of Virginia Apgar is also put into context. It is to my shame that I had forgotten that she was an anaesthetist. I also learned the true significance of *anesthesia à la Reine*. I had not fully appreciated until reading this account that John Snow's technique involved administration of chloroform in sub-anaesthetic concentrations to produce amnesia and analgesia The amount of anaesthetic was varied according to individual circumstances and controlled by careful clinical observation. This was in marked contrast to the practice of some of Snow's contemporaries. Older anaesthetists will recall the use of self-administered trichloroethylene to achieve a similar effect, while younger colleagues may remember the experimental use of enflurane and isoflurane for the same purpose. Queen Victoria had chloroform for her deliveries in 1853 and 1857 and the title of this book is her remark on hearing that her eldest daughter, Vickey, had also been given chloroform when she had her first child in 1859. The view that pain was a necessary concomitant of childbirth, and that to provide analgesia was meddlesome, might have prevailed had it not been for Victoria's involvement.

There are 41 pages of notes at the end of the book, so those who wish to review the author's sources can do so. The reader is therefore not distracted from the main text by a plethora of references and footnotes. There is also a useful index.

This is certainly not a book which needs to be on the reading list of trainees preparing for the FRCA, nor can I recommend that every library should have a copy. There are more useful books to spend limited resources on. However, obstetric anaesthetists who wish to understand the complexities of the responses to pain during childbirth will find something of interest in its pages, as will those who enjoy exploring the history of our specialty

A.P. Madden

Chronic and Recurrent Pain in Children and Adolescents. P.J. McGrath and G.A. Finley (editors). Published by IASP Press, Seattle. Pp. 275; indexed; illustrated. Price $67.00 (IASP members $43.55).

This is a multidisciplinary, multi-authored book, its content coming from an international meeting on paediatric pain held in September 1998 and organized by the editors. It forms volume 13 of the *Progress in Pain Research and Management* series published through IASP Press, which aims to publish low-cost, high-quality books accessible to all. Each chapter is written by an expert in the field and gives a concise overview of the subject under the headings aetiology, factors affecting the disease process, treatment and outcome. As with many multi-authored books, there is variability in the clarity of the writing, although the content of each chapter is excellent. The book also has a North American flavour when talking about socio-economic groups and the problems of health care system funding.

The first four chapters set the scene by relating what we know about the effects of early pain experience and its treatment or non-treatment. It relates the findings from animal work and from the many studies examining human development after pain in the immediate neonatal period.

The major part of the book is devoted to the most important types of chronic pain seen in children. Each chapter is concise, well written and extensively indexed. Gunnar Olsson's chapter on neuropathic pain particularly stands out, containing good clinical advice on how to deal with the problems The penultimate chapter is also interesting, looking at work done on the effect of gender variation and a child's pain It tells us what we always knew, that women complain more about pain than men, but it also tries to

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

explain why this occurs and presents reasons as to why it may be a false finding. Finally, the last chapter looks at the drugs used to treat chronic pain in children. Many treatments are extrapolated from adult practice and do not always work well; there may be a reluctance to use some drugs in children long term. There are still gaps in our understanding of pain neurobiology and a lack of high quality paediatric clinical studies to determine treatment effectiveness.

The main omission of the book is a discussion of chronic pain assessment, the different tools which may be used, their efficacy and failings. However, overall this is an excellent read and I would recommend it to anyone whose practice involves managing pain in children. Although not a comprehensive work on chronic pain in children, it forms an excellent starting point.

M. Cunliffe

Atlas of Applied Pulmonary Physiology. R.M. Wahbe (editor). Published by Zeneca Pharma, Canada. Indexed; illustrated.

The preface by Professor David Bevan sets the scene for the reader. In the introduction, the editor, Richard Wahbe, sets out his goal which is to deliver current knowledge using many illustrations allied to brief and appropriate text written by international authors. This is certainly achieved in the chapter on the control of breathing and the influence that anaesthesia can exert.

There is a good review on the prediction of difficult laryngoscopy and the methods available to overcome this problem. The use of fibreoptic endoscopy and modern radioimaging techniques clearly show that airway obstruction in an otherwise normal patient occurs mainly at the soft palate and epiglottis. The influence of the autonomic nervous system on lung anatomy and function is very revealing.

The basic physiology and mechanical properties of the lung are particularly well illustrated and accompanied by a similar quality text. The pulmonary circulation is examined in equal detail as are the aetiologies that produce pathologies (e.g. pulmonary oedema).

There are interesting treaties on chest wall mechanics, how inspired gases are distributed and the changes that anaesthesia can produce, particularly in regard to *V/Q* mismatch. The brief chapters on oxygenation and carbon dioxide elimination are well worth reading and are an excellent introduction to the chapter on one lung anaesthesia (OLA). This chapter is essential reading for those involved in thoracic anaesthesia, as it is brief, very informative and well written.

There follow several excellent chapters which combine physiology with clinical matters. They also deal with pain relief and the influence that such relief has on pulmonary function. There are well thought out and well-illustrated sections on cardiac physiology. The interactions between spontaneous and artificial ventilation are discussed and are of excellent value.

Finally, there is a short chapter on ARDS. It describes not only the pathophysiology but also discusses, albeit briefly, the various risk scores that are available to judge initial severity so that progress can be monitored.

This book is excellent value and each department library should have a copy The layout is interesting although the proof reading could be improved to eliminate irritating mistakes (e.g. cardiac putput!). In addition, the references are all combined together in the last few pages and could prove inconvenient for the reader who wishes to follow both text and references. However, apart from those minor criticisms, Richard Wahbe must be congratulated on producing such an excellent book. In addition, the generosity of Zeneca Pharmaceutical in supporting this excellent book must be applauded.

R.S. Vaughan

Erratum

Dose-dependency of intra-articular morphine analgesia (BJA 1999; 83: 241–4)

The key to figure 2 was incorrect. The correct figure is given below. The authors apologize for this error.

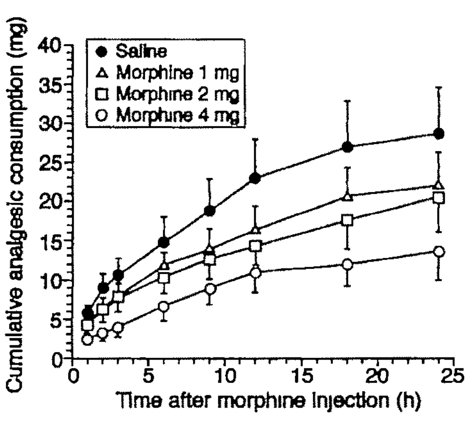


Fig 2 Cumulative analgesic consumption of piritramide after intra-articular injection of saline and morphine 1 mg, 2 mg and 4 mg in patients undergoing arthroscopic knee surgery. Data are mean (SEM)

British Journal of Anaesthesia 84 (1): 131–7 (2000)

BJA

Extended Guide to Contributors*

This is a revised version of the Extended Guide to Contributors which appeared in the Journal in 1990. It should be read in conjunction with the formal Guide to Contributors (in all issues of the Journal). It is intended to advise contributors on the preparation of manuscripts, particularly those who are preparing manuscripts for the first time.

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Aims of the Journal

The *British Journal of Anaesthesia* publishes original work in all branches of anaesthesia, including the application of basic sciences. In addition, the journal publishes review articles, case reports and reports of new equipment.

Some reasons for difficulty

There are several principal reasons for rejection of papers:

(1) *Poor experimental design or inadequate investigation* (or both). Detailed guidance on this aspect is beyond the scope of the present document but inadequate sample size and/or insufficient power are common faults.

(2) *Bad presentation.* This results from inexperience in writing scientific or clinical reports. Various manifestations of the problem may be combined in one manuscript. These include:

(a) Failure to conform to the accepted layout of a scientific paper (see page 132).

(b) Failure to distinguish between jargon and technical terminology (see appendix).

(c) Excessive verbosity. Most manuscripts may be reduced by at least 30% with advantage.

(d) Unsatisfactory or confusing presentation of data in tables or figures (see pages 135, 136).

(3) *Poor English style and syntax.* Although journals are not sympathetic to this problem in papers from the English-speaking countries, *British Journal of Anaesthesia* has a long tradition of helping authors from other countries. Inevitably, however, the provision of this help causes delay.

(4) *Insufficient material.* Try not to break down studies into the smallest publishable units.

Guidance for the early stages

Before beginning to write, analyse your objectives carefully.

What is the question which you have tried to answer?

What message is to be conveyed?

Do the data and your interpretation of them justify the message?

It is recommended that guidance is obtained from colleagues experienced in research and in writing scientific manuscripts.

Statistical analysis is usually an essential component of the process of assessing the validity and implications of any results presented in a paper. Initial statistical advice should be sought before, rather than after, the data have been collected. Do not use 'recipes' for statistical analysis which you do not understand. Do not use the methods of the professional statistician unless you have a reasonable understanding of what they mean.

Do not assume that *figures* that have been prepared for audiovisual presentation will be suitable for publication in a journal; the dimensions are nearly always unsuitable for the printed page (see below).

Consult recent issues of the *British Journal of Anaesthesia* and try to find a paper which conforms, in general format, to the paper you plan to write.

Please make sure that the *legal considerations* which are noted in the formal Guide to Contributors have been fulfilled. It is important to remember also that the internationally agreed code on the ethics of human experimentation (Helsinki Declaration) should be adhered to. A breach of this code will result in automatic rejection. *It is essential to state that local Institutional Ethics Committee approval and informed patient consent have been obtained, where appropriate.* When studies have been conducted in animals, it is essential to indicate the appropriate Home Office Licence number in the United Kingdom or note that approval has been granted by local Animal Research Committees in other countries.

Submission of manuscripts

British Journal of Anaesthesia participates in a uniform requirement agreement on submission of manuscripts (Inter-

---

*Copies of this Extended Guide may be obtained from the Editor-in-Chief's Office.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

national Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to Biomedical Journals. *BMJ* 1988; **296:** 401–405).

Manuscripts must be accompanied by a covering letter signed by all the authors. This should include: (a) Information on prior or duplicate publication or submission elsewhere of *any part* of the work. Please note that it is unethical to submit the same complete work to two journals simultaneously; a clear rejection by an editor is required before submission to a second journal should be considered; (b) a statement of financial or other relationships that might lead to conflict of interests; (c) a statement that the manuscript has been read and approved by all authors; (d) the name, address, telephone number, fax number and email address, if applicable, of the corresponding author who is responsible for communicating with the other authors about revisions and final proofs.

Four copies of each manuscript (including revised texts unless instructed otherwise by an editor) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Please do not staple the manuscript but use a paper clip. Contributors should retain a copy in order to check proofs and in case of loss. Manuscripts should only be submitted on disk when an editor requests it. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. At least one set of figures must be unmounted glossy prints (see below); the other three sets may be photocopies. Annotate photographs as necessary.

The typical layout of the manuscript is:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page *one*, etc. Start each section on a separate page. For a Short Communication see page 136.

Title page

A separate page which includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such a 'A new method of scavenging'. Titles in the form of a question, such as 'Is halothane teratogenic?', are often acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. An author's present address, differing from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers ($^{1\ 2\ 3}$ etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

A short running title containing not more than 50 characters (including spaces) should be included.

Summary

This should appear on the second sheet and should be presented as *one paragraph* in fewer than 250 words. In many respects the summary is the most important part of the paper because it must give the broad objectives of the enquiry, the principal findings and the essential conclusions. Although the reasons for the investigations may be stated, do not give an extensive review. Give the methods of study, in outline only, together with the principal positive findings and any important negative findings. The main numerical data and probability values should be presented concisely. List the main conclusions, but do not discuss the conclusions and more complex issues. Statements such as 'the significance of these results is discussed' are unhelpful. Only in exceptional circumstances is it appropriate to cite references. Abbreviations, other than the standard abbreviations (see below), should appear in the summary only *after* the term has been defined, and only if the term is to be repeated in the summary. In such circumstances, the term should be given once again in full in the text of the paper, with the abbreviation (in parentheses) following.

Keywords

Three to five keywords should be included on the summary page under the heading Keywords. The system used by the journal follows closely that devised by Greene (see *Key Words in Anesthesiology*, ed. Greene NM, 3rd Edn. Amsterdam: Elsevier, 1988).

Introduction

The introduction should give a *concise* account of the background of the problem and the object of the investigation. It should clearly state the aims of the study. Previous work should be quoted only if it has direct bearing on the present problem. For example, a description and evaluation of a system for scavenging anaesthetic gases from an operating theatre need not include an account of the previous literature of the problems of operating theatre contamination by anaesthetic gases and the many studies of morbidity, etc. which may or may not be associated with such contamination. As a rule, the introduction to a paper should not require more than about 200 words.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

Methods

The title of this section may be 'methods', 'materials and methods' or 'patients and methods'. Under no circumstances should the terms 'patients' and 'materials' be regarded as interchangeable. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). When a manufacturer is unlikely to be known to readers of the journal, the address should be provided also. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Drugs. When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. diazepam 0.1 mg kg^{-1}). Do not confuse drug dose with concentration.

Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Patients. Data on the mean age (range), weight, sex, height, criteria for selection, etc. should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Anaesthesia. Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words:

The patients were premedicated with either morphine 10 mg and atropine 0.6 mg (group A) or diazepam 10 mg (group B), both given 1 h before operation. Anaesthesia was induced with thiopental [give rate of injection where appropriate], in a dose sufficient to abolish the eyelash reflex. Succinylcholine 80 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with halothane 0.5–1.0% and nitrous oxide 60% in oxygen, the patient breathing spontaneously from a Magill system. A similar description should be used for animal anaesthesia.

Statistical analysis. Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value. If appropriate a power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change.

Additional guidance on statistics may be obtained from Guidelines for Statistical Reporting in Articles for Medical Journals (Bailar JC, Mosteller F. *Annals of Internal Medicine* 1988; **108:** 266–273).

Results

Description of experimental results should be concise. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. It is not usually necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. The editor has the right to request sighting of the original data collected. As a rule, the following general approach should be adopted:

(1) Prepare all the data in the form of tables.
(2) Decide which data are to be presented in the communication.

(3) Can the essential data be presented succinctly in the text? If not, the essential tables or simplified tables should be prepared.

Tables are important communications and should be accompanied by a legend which makes the table self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

Graphs and histograms based on the results should be considered only in the following circumstances:

(1) where a figure will present the data more clearly than is possible in a table.

(2) when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

For more detailed guidance on the format of presentation of results, the reader is referred to previous issues of the journal. A common example, however, occurs in the case of a comparison of the findings in two groups of patients who have been treated with different drug regimens. The following example that required revision is based on a submitted manuscript, with the permission of the authors:

> *First draft*
>
> There were 43 patients in the pethidine group and 41 in the morphine group. Table 2 shows that the two drug groups were evenly matched in terms of age, weight and duration of operation.
>
> Sixty to ninety minutes after the injection, there was a reduction of anxiety score of 2.9 points in the pethidine group (highly significant $P < 0.001$) and a reduction of 1.3 points in the morphine group (significant $P < 0.01$). The difference in the magnitude of the reduction of anxiety between the two groups was not statistically significant. Both groups showed a further significant reduction to normal in the anxiety rating when tested again 24 hours after the operation.
>
> Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Only 12 out of 43 pethidine patients (28%) could remember all three pictures, while 27 out of 40 morphine patients (68%) were able to recall all three picture cards (Table 3). This indicates a significantly greater incidence of amnesia with pethidine than with morphine ($P < 0.01$) using this test. This persisted for 24 hours in three pethidine and five morphine patients.
>
> Local erythema was present in twelve pethidine patients and in ten morphine patients ninety minutes after injection. This disappeared in the pethidine patients but was still present in the ten morphine patients twenty-four hours after surgery ($P < 0.01$).
>
> *Second version*
>
> Forty-three patients received pethidine and 41 received morphine. The groups were similar in age, weight and duration of operation (Table 2). Sixty to 90 min after injection there was a mean reduction in the anxiety score of 2.9 after pethidine ($P < 0.001$) and 1.3 after morphine ($P < 0.01$). The difference between the two groups was not significant. Both groups showed a further significant reduction to the normal range when tested 24 h after the operation.
>
> Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before operation. Only 12 of 43 in the pethidine group (28%) could recall all three pictures, compared with 27 of 40 in the morphine group (68%) ($P < 0.01$) (Table 3). This persisted for 24 h in three patients in the pethidine group and five in the morphine group. Ninety minutes after injection, local erythema was present in 12 of the pethidine group and 10 of the morphine group. This was still present 24 h after surgery only in the 10 who had received morphine.

In the results section there should be no attempt at a discussion of the findings.

Discussion

This requires discipline by the writer for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there. The form of a discussion should normally follow this pattern:

(1) Summary of the major findings.

(2) Qualifying remarks in relation to these findings; for example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.

(3) Succinct comparison of the present data and relevant data from previous studies.

(4) Deductions—which may explain important differences between the data of the present study and the data of previous studies.

(5) Conclusions from the present study. The original contribution to knowledge from the present study is stated.

(6) The implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.

Acknowledgements

It is inappropriate to acknowledge routine assistance from nursing or surgical colleagues without which any form of clinical research would not be possible. It is essential to acknowledge all sources of financial assistance and any conflicts of interest.

References

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* and *Index Veterinarius* journals.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically in the reference list and numbered accordingly in both list and text.

References in text, tables and legend should be identified by Arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or ^{5}<space>^{16} for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Papers which carry a different system of reference will be returned to the authors for re-typing. The scope for major printer's errors in attempting to rectify inappropriate schemes is considerable.

References in the text. If it is considered essential to cite names of the authors of a study in the text (in addition to the identifying number), up to three names should be cited (A; B and C; D, E and F). In the case of four or more authors, 'G and colleagues', 'G and co-workers', 'G and others' are acceptable. The expression '*et al.*' is not used in the text.

An informal reference to previous work (Z's study or Y's study) is permissible only in a paragraph which contains the reference cited formally.

Abstracts that are more than three years old should not be used as references.

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Personal communications should be cited in the text as (Brown AB, personal communication, year). Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. This should be provided in writing with the first submission of the manuscript.

Papers which have been submitted *and accepted* for publication should be included in the list, with the phrase 'in press' replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction. Abstracts should also be sent with the original submission.

Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

There should be a *table of references* at the conclusion of the paper, commencing on a new sheet. It should be prepared as follows. The names and initials of more than six authors and/or editors should be abbreviated to three names followed by *et al.*

A maximum of 30 references is allowed for an original article and 10 for a short communication.

Journals.

Names and initials of six authors (if more than six, list three followed by *et al.*), title of paper, abbreviated title of journal, year of publication, volume number, first and any change in last page numbers:

Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987; **59**: 14–23

Monographs.

Name of author and initials, title of book (italics), number of edition, town of origin, publisher, year of publication, first and any change in last page numbers (if relevant):

Moore DC, *Regional Block*, 4th edn. Springfield, Illinois: Charles C Thomas, 1979

Chapter in a book.

The reference for an article forming part of a book should take the form:

Hull CJ. Opioid infusions for the management of post-operative pain. In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985; 155–79

It is a serious error to include in the list of references items which are not accurate. It is essential, therefore, that authors check the accuracy of all references which have been listed. It is important also to check that the references listed do indeed appear in the text and *vice versa*.

Preparation of tables

All tables should be on separate sheets and accompanied by legends. Legends should be informative but brief and not contain information which is more appropriate to Methods. Tables may also be submitted on disk. It is preferable to present the data not in table format, but in normal text, with columns separated only by tabs. The tables should be numbered consecutively using Arabic numerals. Units in which results are expressed should be given in parentheses at the top of each column and not

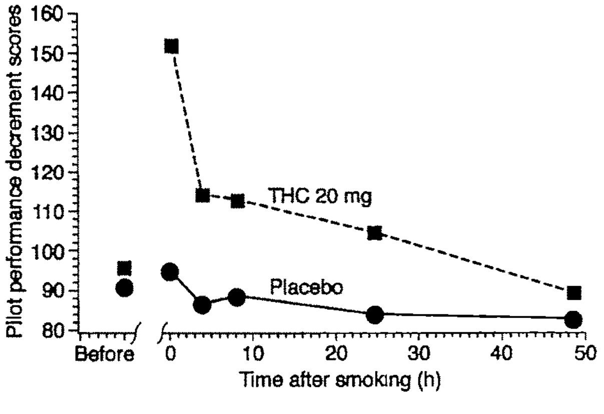


Fig 1 Effect of smoking a cannabis cigarette containing THC 20 mg on pilot performance in flight simulator tasks Performance on six simulator tasks included in one flight session was standardized to give mean decrement scores; nine pilots performed the tasks under both drug and placebo conditions.[76]

repeated in each line of the table. Ditto signs are not used. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that normally used by the journal; in particular, vertical lines should not be drawn. Please be certain that the data given in tables are correct, as changes at the proof stage are particularly expensive.

Illustrations and figures

Photographs should be unmounted glossy prints and should be protected adequately for mailing. Surfaces should not be marred by clips, pins or heavy writing on the back of the photograph.

Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text and using Arabic numerals. Each figure should be accompanied by a suitable legend.

For publication, illustrations are reduced to single column width see Figure 1 (or in case of particularly complex diagrams, to widths between single and double column).

It should be borne in mind that reduction of figures results in an accompanying reduction of boldness (thickness) of all parts of the figure. It is thus inappropriate to use a variety of boldness of axes, graph lines and lettering in one figure, or to present a figure drawn to a large scale in fine lines and with small, fine lettering. The typewriter line thickness of computer printouts to A4 size is thus to be avoided. The problem of computer-produced diagrams may be obviated by programming the computer to produce a diagram of the same size as that of the final published diagram or, alternatively, to produce lines and lettering of large thickness so that photoreduction results in the appropriate size. Photographs and micrographs should be annotated.

Care should be taken that the labelling of axes does not extend the dimensions of the figure substantially. Avoid suppression of the zero point (the axes may be broken (/ /) if required). (*See also* Units, symbols and abbreviations below).

The foregoing advice, which may not be completely intelligible to many authors, will be understood by a professional illustrator whose advice should be sought in most circumstances. It should be emphasized that the dimensions of a figure prepared for a slide are often unsuitable for reproduction on the printed page. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

Magnifications, especially in photomicrographs, should be indicated on the photograph itself by an unlabelled scale bar which would remain appropriate after reduction. Indicate in the legend the length of the bar.

Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below), as alteration to figures or the re-drawing of them by the publisher is an expensive matter and the cost may have to be borne by the author.

Never send figures or photographs unless a suitable version has been retained on file which may be copied easily in the event of loss.

Units, symbols and abbreviations

British Journal of Anaesthesia, in common with other journals in the UK and many other countries, uses the SI system of units with a few notable exceptions (pH and intravascular and ventilatory pressure measurements, which should be given in units of calibration, e.g. mm Hg, cm H_2O). Blood-gas tensions and the partial pressures in the gas phase should be given in the appropriate SI unit (kPa for kilopascal). It is not intended to give a detailed account of the SI system, the notation of units, symbols and abbreviations in this document. Readers are referred to *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors*, 4th Edn. Baron DN, ed. (1988), published by and available from the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE.

Particular problems have arisen in relation to the *notation* of units which was introduced at the same time as the change to the SI system. Avoid the use of the solidus (/) in favour of various units of the expression set on one line. In the case of expressions 'below the line' superscript $^{-1}$, $^{-2}$, etc. as appropriate is given. Thus for drug dosage we write:

$$\text{mg kg}^{-1}$$

A Guide for Biological and Medical Editors and Authors (Baron, 1988) lists also the abbreviations which may be used by authors without previous definition of their meaning. As noted above, all other abbreviations must be defined, once in the summary and once in the text.

In addition, the 'Pappenheimer' system of abbreviations of respiratory terms (Pappenheimer JR, Comroe JH, Cournand A. Ferguson JKW, Filley GF, Fowler WS, Gray JS, Helmholtz HF, Otis AB, Rahn H, Riley RL. Standardisation of definitions and symbols in respiratory physiology. *Federation Proceedings* 1950; **9:** 602–605) is acceptable without definition.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. This does not include preliminary communications. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and Results; Comment.

Size: Not more than 10 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain corespondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

Further reading for authors

While it is hoped that this extended guide to contributors will be of value to those writing for *British Journal of Anaesthesia*, it should not be regarded as comprehensive instruction for those preparing manuscripts. A number of simple texts and papers have been prepared on this subject and it is essential that the author preparing his first manuscript should avail himself of these. We commend particularly Professor Hugh Dudley's book entitled *The Presentation of Original Work in Medicine and Biology*, published by Churchill Livingstone in 1977. In addition, we recommend that authors should be familiar with Eric Partridge's *Usage and Abusage—A Guide to Good English*, published by Hamish Hamilton in several editions. Sir Ernest Gower's *The Complete Plain Words*, revised by Sir Bruce Fraser, is published by Penguin Books and is a treasure-house of common sense in writing. In the matter of spelling, *British Journal of Anaesthesia* follows the *Shorter Oxford English Dictionary*.

Appendix

Common sources of difficulty include the following:

Blood-gases—specify carbon dioxide, P_{CO_2}, etc.

Blood pressure—avoid this term in favour of arterial pressure, etc. Specify mean, systolic, diastolic.

Case—this should not be regarded as interchangeable with the term 'patient'. An account of the management of a patient may be referred to as a 'case history' or 'case report'.

Chronic bronchitics—avoid this expression when you mean patients with chronic bronchitis.

Data—plural.

Demographics—often used incorrectly to refer to patient characteristics.

Due to—avoid unless in the description of a financial debt. *Because of* and *as a result of* are preferable.

Employed—prefer *used.*

Fall and *Rise*—avoid these expressions which suggest a gravitational influence. *Decrease* or *reduction* and *increase* are preferable.

Groups—avoid expressions such as 'thiopental patients' and 'cholecystectomy patients' in favour of 'patients receiving thiopental' and 'patients undergoing cholecystectomy'. It is permissible, however, to refer to the 'thiopental group' or 'cholecystectomy group'.

High and Low—avoid if you mean large and small.

Incidence—this refers to the proportion of a defined group developing a condition within a stated period. *Frequency* is the number of subjects (expressed usually as a percentage) with a condition. *Prevalence* is frequency at one point in time.

Length (of time or drug effect) —prefer *duration.*

Level—avoid in favour of *concentration.*

Multiple adjectives—avoid using an adjective in apposition to a noun, e.g. 'concentration of sodium' is preferable to 'sodium concentration'.

Postoperatively and *preoperatively*—prefer *after operation* or *before operation.*

Postoperative (preoperative) treatment—acceptable.

Relaxants—avoid in favour of 'neuromuscular blocking drugs'.

Rotameter—note capital letter.

Sacrifice—this is ritualism. Killed is preferable.

Showed—prefer *was present* or *occurred.*

Significant—avoid expressions such as 'highly significant' or 'very highly significant', in favour of *significant* with a probability value in brackets.

Sleep-dose—this is vague. Prefer *a dose sufficient to abolish the eyelash reflex*, etc.

Stable (of measurements) —prefer *unchanged* or *virtually unchanged.*

Teflon—note capital letter

Tendency to change—changed.

It is important to avoid conversational expressions such as:

'the patient was ventilated' (the lungs were ventilated)

'the patient was intubated' (the trachea was intubated)

'the patient was placed on a ventilator' (ventilation was controlled artificially)

'the patient was taken off the ventilator' or 'the patient was weaned from the ventilator' (artificial ventilation was discontinued)

'the patient was extubated' (the tracheal tube was removed).

BJA
British Journal of Anaesthesia

International Journal of Anaesthesia: Journal of the Royal College of Anaesthetists

Editor-in-chief
Jennifer M Hunter

Founded in 1923, the *BJA: British Journal of Anaesthesia* remains one of the most authoritative and largest independent journals in anaesthesia.

The *BJA* is the 4th most highly cited anaesthesia journal in the world, and the most widely read anaesthetic journal in Europe.

BJA publishes original articles in all branches of anaesthesia, and emphasis remains on quality and originality, so that the journal only contains papers of the highest standard.

- **Longest established and largest independent European journal of anaesthesia**
- **Consistently high impact factor**
- **Reduced subscriptions for members of IARS, ESA, EACTA, EA and ESRA**
- **Rapid publication**
- **Coverage of all branches of anaesthesia, including the basic sciences**

BJA *British Journal of Anaesthesia*
Tables of Contents and Abstracts **Online**

www.bja.oupjournals.org

Tables of contents and abstracts from current issues of the *BJA* are available at the journal web site.

Alternatively, you can join the e-mail alerting service, to be sent the latest contents each month by e-mail. This service is freely available, just go to **http://www.oup.co.uk/jnls/tocmail** and follow the simple instructions to subscribe.

ORDER FORM

OXFORD
UNIVERSITY PRESS

○ *Please enter my subscription as indicated below*

BJA: British Journal of Anaesthesia,
ISSN 0007-0912 Vols. 84–85, 2000, 12 issues

○ Institutions £217/$346
○ Members of EACT, ESA, IARS, JSA, EAA, ESRA £105/$168
○ Trainees £105/$168 *Please note £ Sterling applies in Europe, US$ elsewhere*

OR

○ I am interested in subscribing, please send me a free sample copy of *BJA International Journal of Anaesthesia*

DELIVERY ADDRESS DETAILS

NAME ______________________________
ADDRESS ______________________________
____
__________ POSTCODE/ZIP __________
COUNTRY ______________________________

PAYMENT DETAILS

○ I enclose the correct remittance
(Please make cheques payable to Oxford University Press)

○ Please charge my Access/Visa/American Express/Mastercard/JCB

CARD NO ______________________________

EXPIRY DATE __________ SIGNATURE __________

If credit card address differs from delivery address, please send details

RETURN ADDRESS

Please return your order form to Journals Marketing, Oxford University Press, Great Clarendon Street, Oxford OX2 6DP, UK Fax +44 (0)1865 267835 Subscriptions can also be placed by telephone using any major credit card Please call the Journals Subscription Department on +44 (0)1865 267907 E-mail jnl.orders@oup.co.uk

In the Americas, please return to Journals Marketing, Oxford University Press, 2001 Evans Road, Cary, NC 27513, USA Fax 919 677 1714 Subscriptions can also be placed by telephone using any major credit card Please call the Journals Customer Services on 1 800 852 7323 (USA and Canada only) or 919 677 0977 (outside of the USA and Canada) E-mail jnlorders@oup-usa.org

BJA

International Journal of Anaesthesia

Volume 84 Number 2 February 2000

EDITORIALS

139 I: Fractured femur in the elderly: intensive perioperative care is warranted
N. E. Sharrock

141 II: Anaesthesia and the nitric oxide–cyclic GMP pathway in the central nervous system
H. F. Galley

CLINICAL INVESTIGATIONS

144 Effect of continuous epidural 0.2% ropivacaine *vs* 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy
H. Jørgensen, J. S. Fomsgaard, J. Dirks, J. Wetterslev and J. B. Dahl

151 Effect of meloxicam on postoperative pain after abdominal hysterectomy
J. P. Thompson, P. Sharpe, S. Kiani and O. Owen-Smith

155 Differential effects of systemically administered ketamine and lidocaine on dynamic and static hyperalgesia induced by intradermal capsaicin in humans
H. Gottrup, P. O. Hansen, L. Arendt-Nielsen and T. S. Jensen

163 Effect of alkalinization of lidocaine on median nerve block
D. G. Ririe, F. O. Walker, R. L. James and J. Butterworth

169 Postoperative pain management and recovery after remifentanil-based anaesthesia with isoflurane or propofol for major abdominal surgery
E. Kochs, D. Côte, L. Deruyck, V. Rauhala, M. Puig, E. Polati, J. Verbist, B. Upadhyaya, C. Haigh and the Remifentanil Study Group

174 Comparison of the incidence of complications at induction and emergence in infants receiving oral atropine vs no premedication
C. A. Shaw, A. A. Kelleher, C. P. Gill, L. J. Murdoch, R. H. Stables and A. E. Black

179 Anaesthetic complications of acromegaly
P. A. Seidman, W. A. Kofke, R. Policare and M. Young

LABORATORY INVESTIGATIONS

183 NOx– concentrations in the rat hippocampus and striatum have no direct relationship to anaesthesia induced by ketamine
J. Wu, T. Kikuchi, Y. Wang, K. Sato and F. Okumura

190 The neuronal nitric oxide synthase inhibitor 7-nitroindazole (7-NI) and morphine act independently on the control of breathing
L. Teppema, E. Sarton, A. Dahan and C. N. Olievier

197 Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia
W. A. C. Mutch, G. M. Eschun, S. E. Kowalski, M. R. Graham, L. G. Girling and G. R. Lefevre

204 Fentanyl protects the heart against ischaemic injury via opioid receptors, adenosine A_1 receptors and K_{ATP} channel linked mechanisms in rats
R. Kato, S. Ross and P. Foëx

215 Halothane attenuates the endothelial Ca^{2+} increase and vasorelaxation of vascular smooth muscle in the rat aorta
H. Tsuchida, S. Seki, S. Tanaka, K. Okazaki and A. Namiki

221 Effects of xenon on cerebral blood flow and autoregulation: an experimental study in pigs
H. Fink, M. Blobner, R. Bogdanski, F. Hänel, C. Werner and E. Kochs

REVIEW ARTICLE

226 Measurement of blood volume in surgical and intensive care practice
J. G. Jones and C. A. J. Wardrop

SHORT COMMUNICATIONS

236 EEG controlled rapid opioid withdrawal under general anaesthesia
M. Hensel, S. Wolter and W. J. Kox

239 Use of microalbuminuria as a predictor of outcome in critically ill patients
K. L. MacKinnon, Z. Molnar, D. Lowe, I. D. Watson and E. Shearer

242 Do blood concentrations of neurone specific enolase and S-100β protein reflect cognitive dysfunction after abdominal surgery?
L. S. Rasmussen, M. Christiansen, H. Rasmussen, P. A. Kristensen, J. T. Moller and the ISPOCD group

245 Adenosine potentiation of neuromuscular blocking agents in guinea-pigs
K. Nitahara, P. Kornak, H. Nagashima, E. S. Vizi, F. F. Foldes and K. Dan

248 Infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy has no opioid-sparing effect
J. R. Klein, J. P. Heaton, J. P. Thompson, B. R. Cotton, A. C. Davidson and G. Smith

250 Propofol decreases stimulated dopamine release in the rat nucleus accumbens by a mechanism independent of dopamine D_2, $GABA_A$ and NMDA receptors
D. Schulte, L. F. Callado, C. Davidson, P. E. M. Phillips, N. Roewer, J. Schulte am Esch and J. A. Stamford

254 The intubating laryngeal mask airway does not facilitate tracheal intubation in the presence of a neck collar in simulated trauma
H. G. Wakeling and J. Nightingale

257 Retrograde nasotracheal intubation with a new tracheal tube: a feasibility study
F. Agrò, J. Brimacombe, D. J. Doyle, L. Marchionni and R. Cataldo

CASE REPORTS

260 Surgery for a fractured femur and elective ICU admission at 113 yr of age
C. D. Oliver, S. A. White and M. W. Platt

263 Thoracic paravertebral block: radiological evidence of contralateral spread anterior to the vertebral bodies
M. K. Karmakar, W. H. Kwok and J. Kew

COMMENTARY

266 Self-citations in six anaesthesia journals and their significance in determining the impact factor
A. Fassoulaki, A. Paraskeva, K. Papilas and G. Karabinis

ABSTRACTS

270P Proceedings of the Anaesthetic Research Society Meeting, University of Edinburgh, November 11–12, 1999

289 CORRESPONDENCE

296 BOOK REVIEWS

298 ACKNOWLEDGEMENT OF ASSESSORS

ANESTHESIA
&
ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists,
the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia,
and the Society for Intravenous Anesthesia

EDITORIALS

1 The Art and Science of Peripheral Nerve Blocks
3 *Anesthesia & Analgesia* in the New Century

CARDIOVASCULAR ANESTHESIA
(Society of Cardiovascular Anesthesiologists)

5 Levosimendan and Myocardial Infarction
12 Aprotinin and Platelets
17 Volatile Anesthetics and Cardiac Eicosanoid Production
25 Sevoflurane and Q-T Interval
28 Hypoxemia in the Supine Position During One-Lung Ventilation
35 Position and Fraction of Inspired Oxygen During One-Lung Ventilation
42 Hypotension, Hyperkalemia, and IV Heparin (Brief Communication)
45 Digital Gangrene After Radial Artery Catheterization in a Patient with Thrombocytosis (Case Report)

PEDIATRIC ANESTHESIA
(Society for Pediatric Anesthesia)

47 Transesophageal Echocardiography and Ventilation in Infants
50 Fetal Cocaine and Myocardial β-Adrenoceptor
57 Cardiac Output Measurement by Arterial Thermodilution (Brief Communication)
59 Epidural: Loss of Resistance—Air and Saline (Brief Communication)
62 Intraoperative Desaturation and Unilateral Breath Sounds During Nissen Fundoplication (Case Report)

AMBULATORY ANESTHESIA
(Society for Ambulatory Anesthesia)

64 Hypnosis and Patient's Perioperative Well-Being

CRITICAL CARE AND TRAUMA

69 Vasopressors During Cardiopulmonary Resuscitation in Severe Hypothermia
74 Acidosis and Gastroduodenal Motility
80 Propofol, *d*-Tubocurarine, and Sepsis
85 Positive End-Expiratory Pressure and CO_2 Elimination
89 NO and Septic Vascular Dysfunction (Review Article)

NEUROSURGICAL ANESTHESIA

102 Endothelin Antagonists and Air Infusion in Dogs
107 Intraoperative Intracranial Pressure Monitoring in Pneumococcal Meningitis (Case Report)

OBSTETRIC ANESTHESIA

109 Pain and Epidural Analgesia
114 Transient Paraplegia After Epidural Anesthesia in a Parturient (Case Report)
116 Prolonged Coma and Quadriplegia After Accidental Subarachnoid Injection of Local Anesthetic with an Opiate (Case Report)

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

119 Distribution of Local Anesthetic During Three-in-One Block
125 Three-in-One Block and Ropivacaine
129 Intraoperative Ketamine Improves Postoperative Analgesia
136 Ketamine and Morphine Tolerance
142 Volatile Anesthetics and Penicillin Status Epilepticus
148 Volatile Anesthetics and Lidocaine Seizure
156 Effects of Pain on Ventilatory Pattern

GENERAL ARTICLES

161 Remifentanil and Change of Bispectral Index After Intubation
168 Recovery After Remifentanil, Desflurane, or Sevoflurane Anesthesia
175 Rocuronium and Perfect Tracheal Intubation
180 Cricoarytenoid Joint Capsule and Relevance to Intubation
186 Dexamethasone and Postoperative Nausea and Vomiting
195 Strain Difference in N_2O Analgesia
200 Chlorocresol for Malignant Hyperthermia Diagnosis
206 Ketamine and Adhesion Molecules
213 Nonimmobilizers Do Not Depress Middle Latency Auditory-Evoked Response

SPECIAL ARTICLE

218 Ernst Trier Mørch

CASE REPORTS

222 Facilitating Submental Endotracheal Intubation with an Endotracheal Tube Exchanger
224 The Prolonged Effect of a Muscle Relaxant in a Patient with Chronic Inflammatory Demyelinating Polyradiculoneuropathy
227 LETTERS TO THE EDITOR
235 BOOK AND MULTIMEDIA REVIEWS

SAMBA PRECONVENTION ISSUE

S
INFORMATIC
INSI

ISSN 0003-2999 Volume 90, Number 1, January 2000

Editorial Board

Editor-in-Chief

J. M. HUNTER, Reader in Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Senior Lecturer in Anaesthesia, *University of Leeds*
D. G. LAMBERT, Senior Lecturer in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. R. ELLIS, Professor of Anaesthesia, *University of Leeds*
W. FITCH, Professor of Anaesthesia, *University of Glasgow*
G. M. HALL, Professor of Anaesthesia, *University of London*
D. J. HATCH, Portex Professor of Anaesthesia, *University of London*
P. HUTTON, Vice-president, *Royal College of Anaesthetists*
R. D. MILLER, Professor of Anaesthesia, *University of California, San Francisco*
I. POWER, Associate Professor, *University of Sydney, Australia*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. SEAR, Clinical Reader in Anaesthesia, *University of Oxford*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Reader in Anaesthesia, *University of Plymouth*
L. STRUNIN, President, *Royal College of Anaesthetists*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Technical Editor

LINDA GOUGH

Please visit the Journals's World Wide Web site at http://bjanaes.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to BJA comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate

Institutions: UK and Europe £217, Rest of World US$346
Trainees: UK and Europe £105, Rest of World US$168
Single issue: UK and Europe £23, Rest of World US$36

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express, Diners, JCB); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; Email: jnl.info@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 80 onwards to* Oxford University Press. *For Vols 1–79* to Dawsons Back Issues, Cannon House, Folkestone, Kent. Tel: +44 (0)1303 203612; Fax +44 (0)1303 203617.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262.

© *The Board of Management and Trustees of the British Journal of Anaesthesia* 2000

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE. or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$346. British Journal of Anaesthesia is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

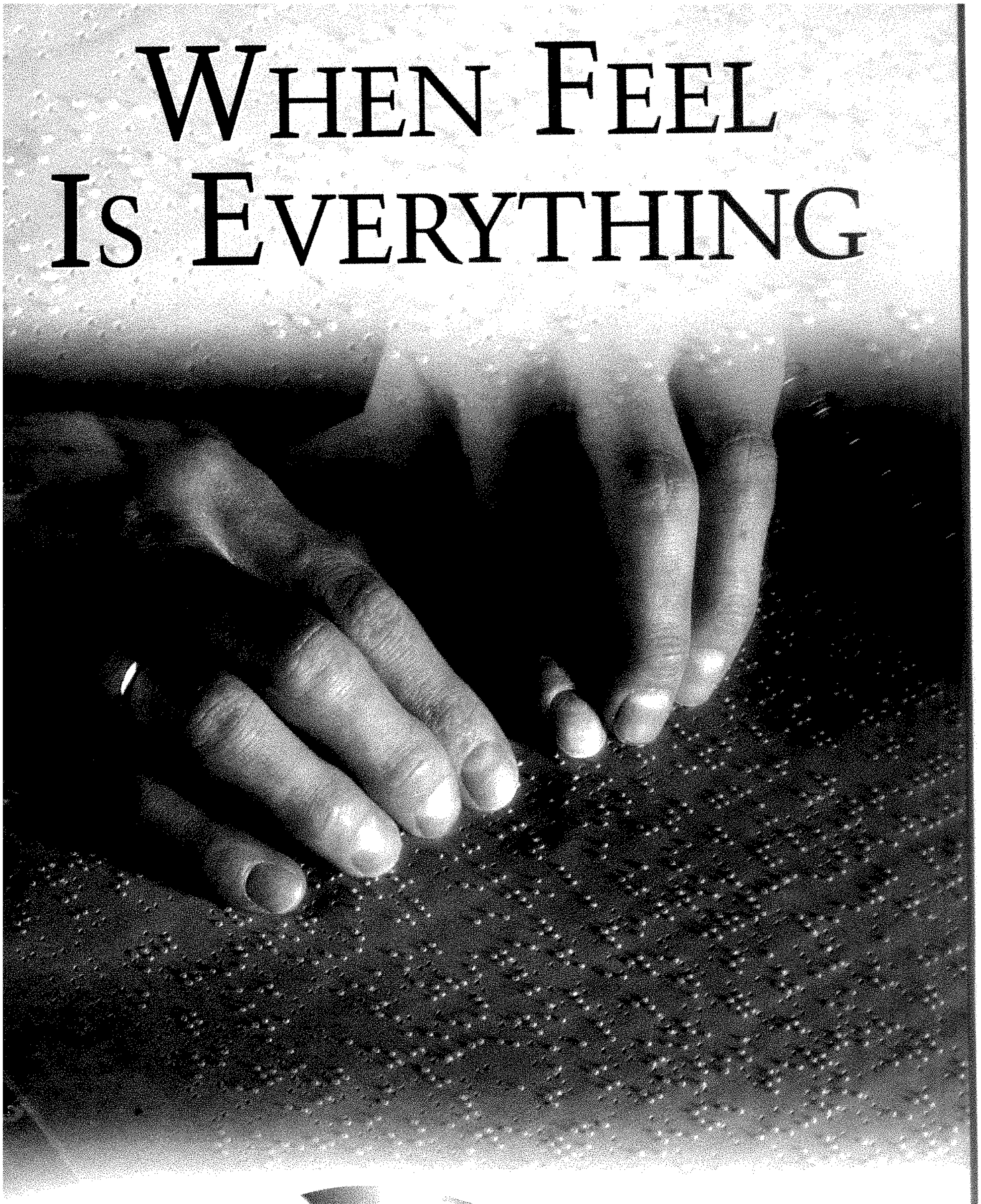
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000



CSEcure

Combined Spinal Epidural Needle System

CSEcure's unique design provides confidence and control without compromising tactile feel.
So when you perform a procedure where feel is everything, feel CSEcure.
Visit our website today: www.portex.com

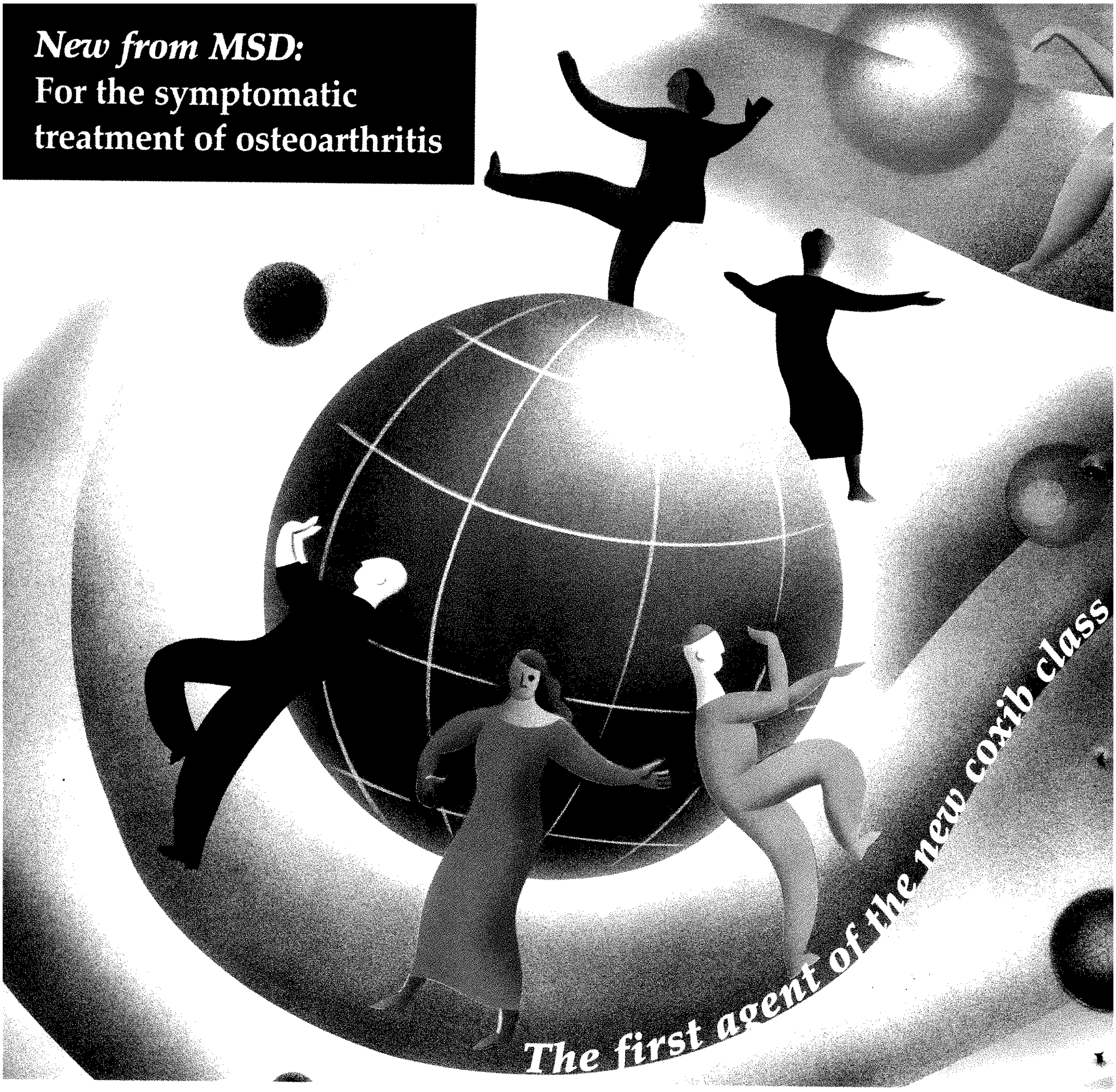
SIMS Portex

For further information, please call SIMS Portex on +44 (0) 1303 260551. SIMS Portex Limited, Hythe, Kent, CT21 6JL, UK. E-Mail: export.sales@portex.com or uk.sales@portex.com

SIMS is a world leading medical manufacturing group, with companies in Europe, North Americ South Africa and the Pacific region, providi innovative products t critical care and community care professionals worldwide.

SIMS
SMITHS INDUSTR
Medical System
INNOVATION IN CRITICAL AN
COMMUNITY CARE

New from MSD:
For the symptomatic treatment of osteoarthritis


The first agent of the new coxib class

VIOXX®▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib.

VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg 5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

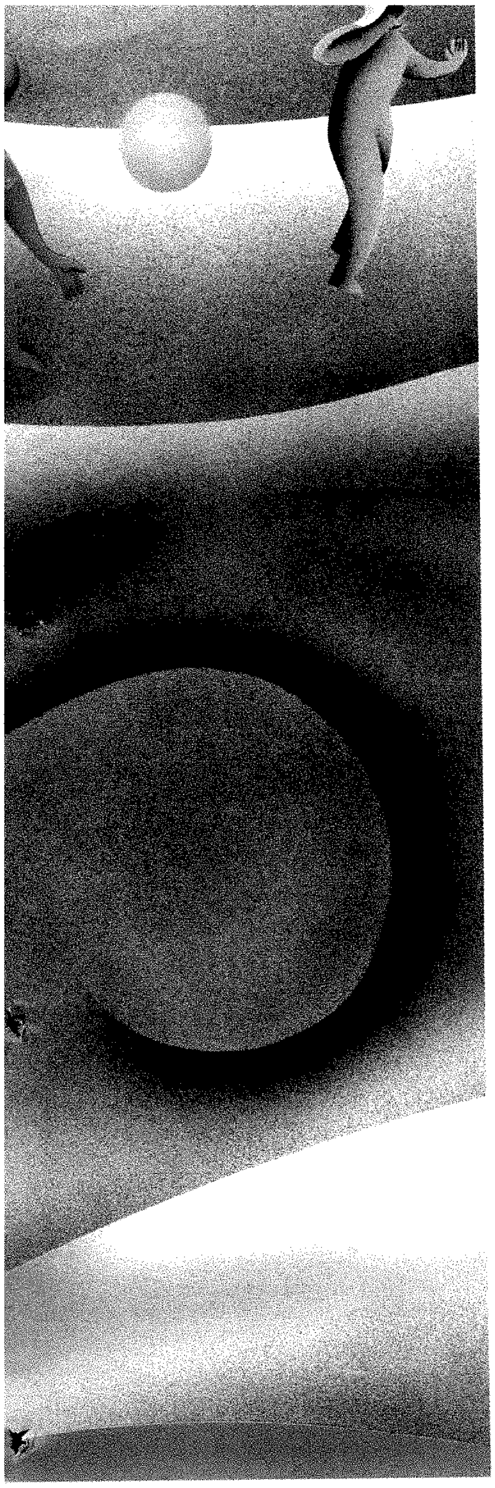
Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib.

Rofecoxib may mask fever

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone. This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1]*

- The power of high-dose NSAIDs – diclofenac and ibuprofen.[2]
- Superior GI safety profile compared to conventional NSAIDs – diclofenac, ibuprofen and nabumetone.[2, 3]
- True once-daily therapy – for a wide range of patients.[2]

* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

TRUE ONCE-DAILY

VIOXX® ▼

(rofecoxib)

Selective. Strong. Simple.

rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** December 1999

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

© Merck Sharp & Dohme Limited 1999. All rights reserved.

References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Laine L, Harper S, Simon T et al. A randomised trial comparing the effect of rofecoxib, a cyclo-oxygenase-2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;117:776-783.

MSD

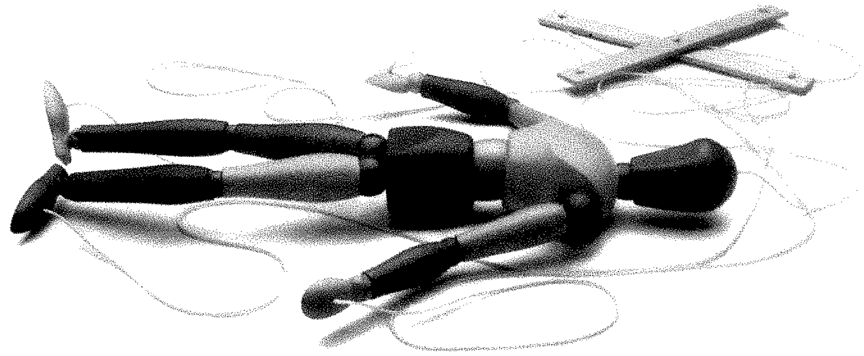
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

05-00 VOX.99.GB.65619.Jf

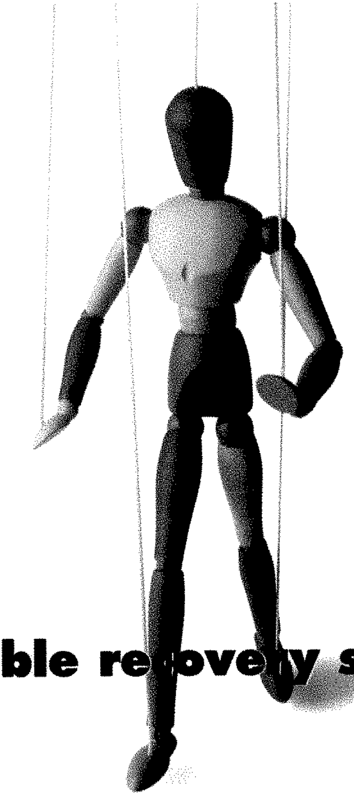
ESMERON

Presentation: 10 mg/ml rocuronium bromide in 5ml or 10ml vials as an aqueous solution for injection. **Other ingredients:** sodium acetate, sodium chloride, acetic acid to pH 4 and water for injections.
Uses: As an adjunct to general anaesthesia to facilitate endotracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.
Dosage and administration: Esmeron is administered intravenously as a bolus or as an infusion. See Summary of Product Characteristics for compatibilities.
Dosage is individualized taking into account method of anaesthesia, duration of surgery, possible interactions with other drugs and the patient's condition. Routine use of appropriate neuromuscular monitoring technique is recommended.
In adults: For short to long lasting surgical procedures:
Intubation: 0.6 mg / kg, Rapid sequence induction 1.0mg/kg,
Maintenance dose: 0.15 mg/kg, (reduce to 0.075mg - 0.1mg/kg for Long-term inhalational anaesthesia).
Continuous infusion: Loading dose 0.6 mg/kg, then infusion rate 0.3 - 0.6 mg/kg/hour or under inhalational anaesthesia 0.3 - 0.4mg/kg/hr. Continuous monitoring of block is essential.
(See Summary of Product Characteristics for advice for intensive care procedures, children, elderly, cirrhotic and overweight patients).
Contraindications Previous anaphylactic reactions to rocuronium or the bromide ion.
Precautions and warnings: Use under the supervision of experienced clinicians familiar with neuromuscular monitoring techniques. Ventilation is mandatory until adequate spontaneous respiration is restored. Dose levels above 0.9 mg/kg may increase heart rate which could counteract bradycardia produced by other anaesthetic agents or vagal stimulation. Hepatic and/or biliary tract disease, renal failure, prolonged circulation time and neuromuscular disease hypothermia and obesity may influence the effects of Esmeron. Severe electrolyte disturbances, altered blood pH or dehydration should be corrected when possible. Clinicians should be aware of the signs and symptoms of malignant hyperthermia
Effect on ability to drive or use machines: Using potentially dangerous machinery or driving are not recommended within 24 hours of full recovery.
Use in pregnancy and lactation: Esmeron should be given to pregnant or lactating women only when the benefits outweigh the risks. Dose in Caesarean section: 0.6mg/kg.
Side effects: Anaphylactic reactions are very rarely seen. No clinically significant tachycardia, hypotension or other clinical signs of histamine release have been reported.
Interactions: Other drugs may influence the effects of non-depolarizing NMBA's, including anaesthetics, other NMBA's, antibiotics and suxamethonium, diuretics, (-adrenergic blocking agents. See Summary of Product Characteristics for details.
Overdose: The patient should continue to be ventilated. When reversal fails ventilation must be continued until spontaneous breathing occurs.
Other Information: A dose of 0.6 mg/kg provides adequate intubation conditions within 60 seconds in nearly all patients, with a clinical duration of 30-40 minutes. General muscle paralysis is established within 2 minutes.
Package quantities: 50mg/5ml (12 vials) 100 mg/10ml (10 vials). NHS Prices 50mg x12 vials - £38.78 100mgx10 vials - £64.63 Legal Category POM Product Licence Number 3524/0025
Further information is available from Organon Teknika Limited, Cambridge Science Park, Milton Road, Cambridge CB4 OFL

Oct 1999



Rapid relaxation gets the applause...



...then predictable recovery steals the show.

An outstanding safety profile in all procedures.

Esmeron has now been used with confidence in over 35 million patients. This confidence is the result of its outstanding clinical profile:

Rapid onset

Esmeron at a dose of 0.6 mg/kg ensures control of the airway within one minute in 95% of patients. Its onset time is faster than that of all available non-depolarizing neuromuscular blocking agents.[1]

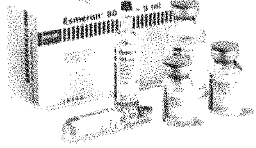
Predictable recovery

Esmeron's spontaneous recovery index is relatively constant, following either single or multiple bolus doses or after use as a long-lasting intravenous infusion.[2,3]

Stable hemodynamic profile

"In contrast to atracurium, mivacurium and tubocurarine, administration of Esmeron caused no significant changes in plasma histamine concentrations or in hemodynamic state at any time."[4]

For full details of this exceptional all-rounder, please contact your local Organon Teknika representative.



1. Puhringer et al. Anesth. Analg. 1992; 75: 37 - 40 **2.** Foldes et al. Exc Med Ams. 1990: 171 - 181 **3.** Sparr et al. Eur J Anaesth. 1994: 11(9): 63 - 65 **4.** Naguib et al. Br J Anaesth. 1995; 75: 588 - 592

organon teknika

ESMERON®
ROCURONIUM BROMIDE

For more information: Organon Teknika bv, Boseind 15, 5281 RM Boxtel, telefoon +31 (0)411 654911, telefax +31 (0)411 654201
Internet: http://www.organonteknika.com

One Year Obstetric Anesthesia Fellowship

Duke University Medical Center
Durham, North Carolina, USA

Want to get further obstetric anesthesia experience/research and enjoy a good climate/lifestyle? This post is for you. The Department of Anesthesiology at Duke University Medical Center invites applications for Fellowship in Obstetric Anesthesia for the academic year beginning July 2000.

Candidates should have FRCA prior to commencing post. Emphasis on clinical research and advanced clinical training in a tertiary center with approximately 3,000 deliveries per year including many high risk consults and referrals. Opportunities to participate in NIH-funded laboratory research as well as clinical outcomes research. Salary $45,000/annum.

Applicants should send a curriculum vitae and 3 letters of reference to Elizabeth Bell, M.D., M.P.H., Fellowship Director, Division of Women's Anesthesia, Department of Anesthesiology, Box 3094, Duke University Medical Center, Durham, NC 27710. Tel: (919) 681-6535, Fax: (919) 681-8357, E-mail: bell0027@mc.duke.edu

Informal discussion encouraged with either Elizabeth Bell, M.D.; or John Booth, M.B., Ch.B., FRCA, E-mail: booth006@mc.duke.edu

---

ISMETT*

HEART/LUNG TRANSPLANT ANESTHESIA AT UPMC PALERMO

**(l'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione)*

The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government to be inaugurated during 2000. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@ anes.upmc.edu

WEST OF SCOTLAND POSTGRADUATE MEDICAL EDUCATION BOARD

SUB-COMMITTEE IN ANAESTHESIA

STUDY DAY ON ANAESTHESIA
EVIDENCE IN INTENSIVE CARE MEDICINE

Thursday 30 March 2000
Kelvin Conference Centre,
West of Scotland Science Park, Glasgow

EVIDENCE IN INTENSIVE CARE MEDICINE

CHAIRMAN:	Dr J Dougall, Consultant Anaesthetist, Western Infirmary, Glasgow
0930 - 1000	Coffee and Registration
1000 - 1030	Evidence, how to find it Dr A Wales, Librarian, Royal Infirmary, Glasgow
1030 - 1100	Original research, how to read it Dr M Daniel, Consultant Anaesthetist, Royal Infirmary, Glasgow
1100 - 1230	Original research, how to organise it Dr P Langhorne, Consultant Physician, Royal Infirmary, Glasgow
1230 - 1300	Evidence, how to present it in Court Dr M Booth, Consultant Anaesthetist, Royal Infirmary, Glasgow
1300 - 1400	Lunch

WHAT IS THE EVIDENCE?

CHAIRMAN:	Dr C Howie, Consultant Anaesthetist, Victoria Infirmary, Glasgow
1400 - 1430	ß-blockade for high risk patients Professor J McMurray, Consultant Cardiologist, Western Infirmary, Glasgow
1430 - 1500	Blood transfusion in Intensive Care Dr M Garrioch, Consultant Anaesthetist, Southern General Hospital, Glasgow
1500 - 1530	Enteral nutrition Dr A Davidson, Consultant Anaesthetist, Victoria Infirmary, Glasgow
1530 - 1600	Swan-ganz catheters Dr J Kinsella, Consultant Anaesthetist, Royal Infirmary, Glasgow
1600 - 1630	Preoptimization Dr O Boyd, Consultant in Intensive Care Medicine, Royal Sussex Hospital

REGISTRATION FEE: £75

Application forms and further information from:
Mrs W E Scott, Administrator,
West of Scotland Postgraduate Medical Education Board,
1 Horselethill Road, Glasgow G12 9LX
(Telephone: 0141 330 5274; Fax: 0141 330 3106;
Email: Wendy.Scott@scpmde.scot.nhs.uk)

ωscpme

McMaster University
Hamilton, Canada

Cardiac Anaesthesia Fellowship

Applications are invited for a Cardiac Anaesthesia Fellowship at Hamilton Health Sciences Corporation, a tertiary regional cardiac centre serving an area from the Niagara Pennisula to the Bruce Peninsula as well as Northwestern Ontario. Annual cardiac surgical volume is over 1,300, providing a full range of cardiac surgical procedures.

Further information is available on the website:

http://www-fhs.mcmaster.ca/anaesthesia/education
or from Mrs Mary Gahagan, Office of the Chair,
Department of Anesthesia, McMaster University,
HSC-2U1, 1200 Main St W, Hamilton,
Ontario, Canada L8N 3Z5
Tel: 01-905-521-2100 ext. 75166
Fax: 01-905-523-1224
E-mail: gahaganm@fhs.mcmaster.ca

Editorial Notices

Primary FRCA Revision Course

Leicester, UK, March 6–8, 2000

This course will take place in the Hermitage Hotel, Oadby, Leicester. It is a 3-day residential revision course with 50% of course time on mock exam practice. The co-ordinator is Dr Donal Buggy.

For further information, please contact:

Mrs Anne Henry, University Department of Anaesthesia, Leicester General Hospital, Leicester LE5 4PW, UK.

Tel: +44 (0) 116 258 4661; Fax: +44 (0) 116 258 4611.

6th America–Japan Anesthesia Congress

Honolulu, Hawaii, March 9–10, 2000

74th Clinical and Scientific Congress of the International Anesthesia Research Society

Honolulu, Hawaii, March 10–14, 2000

75th Clinical and Scientific Congress of the International Anesthesia Research Society

Ft. Lauderdale, Florida, March 16–20, 2001

76th Clinical and Scientific Congress of the International Anesthesia Research Society

San Diego, California, March 16–20, 2002

For further information contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131-2553, USA.

Tel: +1216 642 1124; Fax: +1216 642 1127;
E-mail: iarshq@iars.org; Web: www.iars.org

20th International Symposium on Intensive Care and Emergency Medicine

Brussels, March 21–24, 2000

For further information, please contact:

Mr Carl Vanhaesendonck, Manager, Promotion des Soins Intensifs, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Bruxelles, Belgium.

Tel: +32 2 555 3216; Fax: +32 2 555 4555;
E-mail: sympicu@ulb.ac.be

Anaesthetics Refresher Course

Cape Town, March 25–26, 2000

This meeting will take place at the Education Building, University of Cape Town, South Africa.

For further information, please contact:

Mrs J. Theron, Postgraduate Conference Division, Barnard Fuller Building, UCT Faculty of Medicine, Anzio Road, Observatory 7925, Cape Town, South Africa.

Tel: +27 21 406 6911; Fax: +27 21 448 6263.

South African Society of Anaesthesiologists Congress

Cape Town, March 26–30, 2000

This meeting will take place at the Baxter Theatre Complex, Rondesbosch, Cape Town.

For further information, please contact:

Mrs J. Theron, Postgraduate Conference Division, Barnard Fuller Building, UCT Faculty of Medicine, Anzio Road, Observatory 7925, Cape Town, South Africa.

Tel: +27 21 406 6911; Fax: +27 21 448 6263.

8th Annual Congress of the European Society of Anaesthesiologists

Vienna, Austria, April 1–4, 2000

The congress will be held in the Austria Center.

Abstract deadline is December 1, 1999.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Diagnostic Imaging of the Shoulder, Elbow and Wrist Joints: A Radioclinical Challenge

Genval (Brussels), April 28–29, 2000

The symposium is sponsored by the GETROA (Groupe d'Etude et de Travail en Ostéo-Articulaire). The specific aims of the symposium are: to summarize the current state of knowledge on shoulder, elbow and wrist imaging using state-of-the-art techniques; to establish consensual algorithmic approaches for diagnosing of upper extremity pathology, formulating on this basis recommendations to the medical community; to discuss unsolved clinical problems and potential solutions based on current clinical and imaging knowledge; and to explore future directions of investigations.

December 31, 1999 (deadline for submission of abstracts).

For further information, please contact:

F. Schuind, MD, PhD, Department of Orthopaedics, Erasme

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium.

Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail: fschuind@ulb.ac.be

Final FRCA Course

Leicester, May 2–5, 2000

The course will take place at Glenfield Hospital, Leicester and includes lectures, tutorials, mock vivas, mock examinations and video-recorded vivas.

Places are limited so please apply early.

Course fees: £220.00

For further information please contact:

Mrs C. Gethins, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Tel: +44 116 258 5291; Fax: +44 116 285 4487; E-mail: chg2@le.ac.uk. Details also on departmental web page: www.le.ac.uk/anaesthesia.

German Congress of Anaesthesiology 2000

Munich May 6–9, 2000

For further information, please contact:

Nadja Schwarz, Project Managment, Medizinische Congressorganisation Nürnberg GmbH, Wielandstraße 6, D-90419 Nürnberg, Germany.
Tel: +49 911 39 3160; Fax: +49 911 33 1204; E-mail: mcn@mcn.nuernberg.de
www:http//www.mcn-nuernberg.de

5th Congress of the European Resuscitation Council 'Resuscitation 2000'

Antwerp, June 1–3, 2000

Congress Director: Prof. Dr Leo Bossaert

For further information, registration and abstracts, please contact:

ERC secretariat, PO Box 113, 2610 Antwerp, Belgium.

Tel: +32 3 821 36 16; Fax: +32 3 828 48 82; E-mail: erc@uia.ua.ac.be; Website: http://www.erc.edu.

For hotel reservation and tours, contact:

Medicongress, Waalpoel 28/34, 9960 Assenede, Belgium.

Tel: +32 9 344 39 59; Fax: +32 9 344 40 10; E-mail: ERC2000@medicongress.com; Website: http://www.medicongress.com/erc.

*Pre-congress courses in BLS, AED, ALS, PLS on May, 29–31, 2000.

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

World Paediatric Anaesthesia Meeting

Nova Scotia June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

New Perspectives in Pain Relief

Leicester, September 21–22, 2000

The Department of Anaesthesia and Pain Management, University of Leicester, in association with the *British*

ESA

EUROPEAN SOCIETY
OF ANAESTHESIOLOGISTS

AUSTRIAN SOCIETY
OF ANAESTHESIOLOGY
RESUSCITATION AND
INTENSIVE CARE MEDICINE

ÖGARI

IN COOPERATION WITH
THE EUROPEAN ACADEMY OF
ANAESTHESIOLOGY

JOIN US IN VIENNA

1-4 APRIL 2000

8th ESA Annual Meeting with the Austrian International Congress

Symposia, Refresher Courses, Workshops, Industrial Symposia and Exhibition,
Free Presentations (oral and poster discussions)

English and German language sessions

ESA SECRETARIAT
32 AV. DE TERVUREN - BTE 30
B-1040 BRUXELLES BELGIUM
PHONE +322 743 32 90
FAX +322 743 32 98
E-MAIL: esa@euronet.be
WEB: www.euroanesthesia.org

ÖGARI SECRETARIAT
JOH. NEPOMUK VOGL-PLATZ 1
A-1180 VIENNA AUSTRIA
PHONE: +431 406 48 10
FAX: +431 406 48 11
E-MAIL: oegari@oegari.at
WEB: www.oegari.at

Deadline abstracts: October 15, 1999

AMA Category I CME Accreditation

Journal of Anaesthesia, will be holding a meeting on new perspectives in pain relief.

The meeting coincides with 21st anniversary of the founding of the Academic Department of Anaesthesia in Leicester.

For further information, please contact:

Mrs C Gethins, University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Tel: +44 (0) 116 258 5291; Fax: +44 (0) 116 285 4487.

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl.

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)

Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

12th World Congress of Anaesthesiologists
Montréal, Canada • June 4 - 9, 2000

To receive registration information for this important world congress,
please contact the Congress Secretariat
c/o Events International Meeting Planners Inc.
759 Victoria Square, Suite 300, Montréal, Québec, Canada H2Y 2J7
Tel.: (514) 286-0855, Fax: (514) 288-7945, E-mail: info@eventsintl.com or visit our Web site: http//www.wca2000.com

Centre universitaire de santé McGill
McGill University Health Centre

Université McGill
McGill University

ENDOWED PROFESSOR AND HEAD OF PAEDIATRIC ANAESTHESIA
McGILL UNIVERSITY HEALTH CENTRE

The McGill University Health Centre and the Montreal Children's Hospital invite applications for the newly established position as an Endowed Professor in Paediatric Anaesthesia.

As a recognized and academic leader in Paediatric Anaesthesia, you will have the opportunity to share your vision and utilize your leadership skills in the development of teaching, research and clinical service programs. You will lead a young and dynamic group of anaesthesiologists at the Montreal Children's Hospital which is part of the McGill University Health Centre.

As a forceful leader, you will be expected to assure paediatric anaesthesia services of excellence, in which fellowship programs for subspecialty training are established and you will be instrumental in research development. Laboratory facilities for research will be available and appropriate financial support provided.

Anticipated start date is July 1, 2000.

Applications, including a curriculum vitae and the names and addresses of three referees, should be directed to: Dr. Franco Carli, Professor and Chairman, Department of Anaesthesia, McGill University, 687 Pine Avenue West, Room F9.08, Montreal, Quebec H3A 1A1, Tel: (514) 842-1231 x.5345, Fax: (514) 843-1488 and E-mail: mdfc@musica.mcgill.ca

In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents of Canada. McGill University is committed to equity in employment.

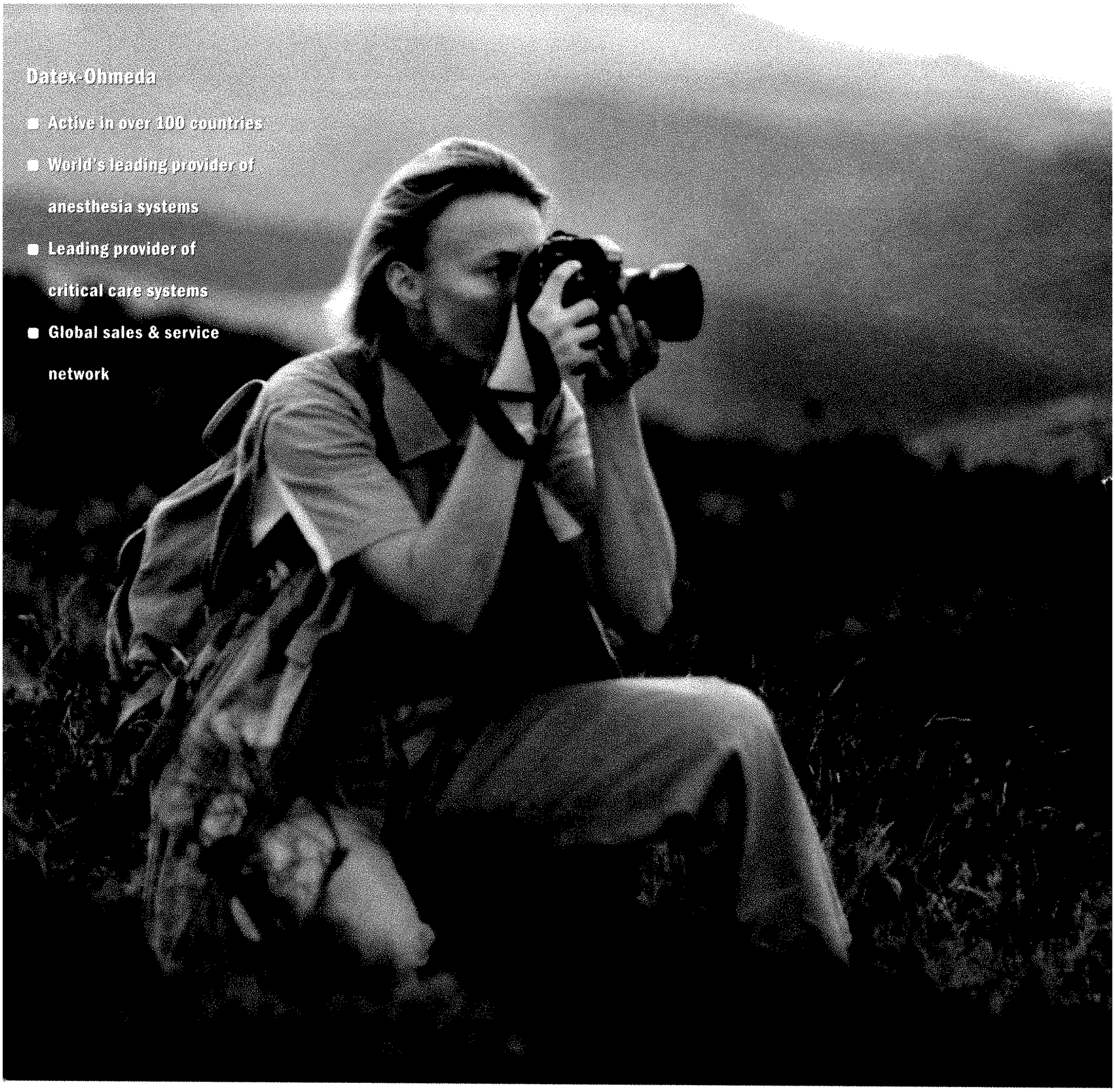
OXFORD JOURNALS ADVERTISING

To advertise in this publication contact
Peter Carpenter

PRC
ASSOCIATES

Advertisement Managers

THE ANNEXE, FITZNELLS MANOR
CHESSINGTON ROAD, EWELL VILLAGE, SURREY KT17 1TF, UK
TELEPHONE: +44 (0)181-786 7376   FAX: +44 (0)181-786 7262
EMAIL: mail@prcassoc.co.uk



Datex-Ohmeda

- **Active in over 100 countries**
- **World's leading provider of anesthesia systems**
- **Leading provider of critical care systems**
- **Global sales & service network**

Moments in focus

The photographer's talent is being in the right place and time. Where her ability to focus finds the essential. For over 100 years, our place has been the clinical environment. Where we focus on the real needs of healthcare professionals.

We are Datex-Ohmeda.

The world's leading provider of anesthesia systems. An important provider of critical care systems. We are now ready to make anesthesia and critical care work as one – solutions at the heart of the entire care process.

Datex·Ohmeda®

Devoted to caring for life

www.datex-ohmeda.com

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 84, Number 2, February 2000

Editorial I

Fractured femur in the elderly: intensive perioperative care is warranted

A case report in this month's issue of the *British Journal of Anaesthesia* describes the in-hospital management of the oldest living Briton, who at 113 yr sustained a fractured femur.[1] The initial plan was to confine her to bed (to die), but after 8 days of unsatisfactory care, she was operated on successfully, received intensive care after surgery and was discharged home. This case highlights several clinical issues, including whether it is appropriate *not* to operate on these patients and how intensive the care should be. It raises a number of ethical issues for physicians and society, in addition to immense economic implications.

The problem of treating fractured femurs in the elderly is immense. In 1990, it was estimated that 1.7 million patients worldwide had a femoral neck fracture[2] and there were 300 000 in the USA.[3] It is difficult to estimate the costs as they vary among countries, but in 1988, each elderly patient cost between $35 000 and $38 000 to treat in the USA.[2] It is the very elderly who pose the greatest risk and the proportion of the very elderly is increasing. For example, in New Zealand, the proportion of patients treated for femoral neck fracture who were more than 85 yr old was 17% in 1905, 40% in 1987 and it is projected that by 2011 the proportion will be 65%.[4] It is the very elderly (patients over 80 yr) who pose the greater perioperative risk,[5 6] have the highest 1-yr mortality and are least likely to be independent after hip fracture.[7] Remarkably, in spite of the enormity of the problem, little attention is directed towards these patients in the anaesthetic literature.

There appears to be a reluctance to treat these patients aggressively; in a sense, they are being 'red-lined'. There are several reasons: they are mainly elderly, non-working members of society; they are often living alone or in nursing homes; many are medically ill; and 27% are admitted to nursing homes after the fracture.[7] Finally, there may be concerns over the liability of audit consequences if the patient dies in the operating theatre.

Published numbers suggest that many of these patients die within a year of the fracture.[3 5 7] In the USA, 1-yr mortality is 24% overall with 4% in-hospital death.[3] Dementia, ASA category and age influence mortality age.[3 5] Mortality may be 4–5 times higher in ASA III and IV patients than in ASA I and II patients.[8] Risk of dying within 12 months is about 10% in patients aged 60–69 yr, increasing to 50% in the over-90-yr-old group.[5] Most of the excess mortality in the elderly occurs in the first 6 months after surgery.[7]

However, better anaesthetic and perioperative care with aggressive rehabilitation may improve outcome. Surgeons who perform more hemiarthroplasties for fractured hip have lower rates of complications and mortality, and reduced length of hospital stay.[9] Hospitals which perform more surgery for fractured hip likewise have a lower mortality,[10] and major teaching hospitals in the USA have about a 40% lower mortality than others.[11] These data suggest that optimal care may reduce cost and improve outcome.

The experience at the Cornell Medical Center is interesting in this regard. A 1-yr follow-up of 68 patients more than 90 yr old who had repair of a fractured hip at New York Hospital (a large acute care teaching centre of the Cornell Medical Center) was performed. One patient died in-hospital and two during the next year (Charles N. Cornell, MD, personal communication). At the Hospital for Special Surgery, an elective orthopaedic hospital within the Cornell Medical Center, most fractured femur patients receive regional anaesthesia, radial artery and central venous pressure monitoring, 12–24 h of high acuity care, and intensive early rehabilitation. Many receive low-dose epidural analgesia for 24–48 h, which may enhance rehabilitation as has been shown for total knee arthroplasty.[12–15] Over the past 3 yr, the in-hospital mortality was 1.5% (three of 204). These data suggest that more intensive expert care may lower perioperative mortality following a fractured hip. The 113-yr-old patient reported in this month's *British Journal of Anaesthesia* ultimately received intensive therapy and was discharged home.[1]

How should one handle the elderly and medically complex patient with a fractured femur? Leaving these patients in traction and administering systemic opioids is an unacceptable option—'conservative measures were ineffective and the patient was confined to bed in pain with no chance of survival'. This mode of treatment is not only ineffective but also inhumane as patients develop contractions of the hip, bedsores and die slowly of sepsis, pneumonia or pulmonary emboli.[16] Finally, from an economic point of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

view, this has to be very expensive and occupies hospital beds for weeks, limiting access to healthcare for other patients.

What is the best way to proceed when the very elderly and sick patient with a fractured hip enters hospital? It is my belief that they should be operated on as soon as it is feasible. Delaying surgery to medically optimize patients may be detrimental, as the metabolic response to the injury does not begin to resolve until the fracture is stabilized.[17] Merely administering a general anaesthetic by a junior staff member and returning them to the ward to see how they do is probably suboptimal.

It is time to reassess the approach to fractured femur in the elderly. If outcome can be improved with aggressive perioperative care, it behoves both orthopaedic surgeons and anaesthetists to take a more involved approach to these cases (as was eventually done in this 113-yr-old patient). It might also surprise the healthcare economists to discover that better care is cheaper because it avoids complications.

N. E. Sharrock
Department of Anesthesiology
The Hospital for Special Surgery
535 East 70th St
New York, NY 10021, USA

References

1 Oliver CD, White SA, Platt MW. Surgery for fractured neck of femur and elective ICU admission at 113 yr of age. *Br J Anaesth* 2000; **84**: 260–2

2 Johnell O. The socioeconomic burden of fractures: today and in the 21st century. *Am J Med* 1997; **103**: 20S–5S (discussion 5–6S)

3 Wolinsky FD, Fitzgerald JF, Stump TE. The effect of hip fracture on mortality, hospitalization, and functional status: a prospective study. *Am J Public Health* 1997; **87**: 398–403

4 Rockwood PR, Horne JG, Cryer C. Hip fractures: a future epidemic? *J Orthop Trauma* 1990; **4**: 388–93

5 Schrøder HM, Erlandsen M. Age and sex determinants of mortality after hip fractures: 3,895 patients followed for 2.5–18.5 years. *J Orthop Trauma* 1993; **7**: 525–31

6 Aharonoff GB, Koval KJ, Skovron ML, Zuckerman JD. Hip fractures in the elderly: predictors of one year mortality. *J Orthop Trauma* 1997; **11**: 162–5

7 Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med* 1997; **103**: 12S–7S (discussion 7–9S)

8 White BL, Fisher WD, Laurin CA. Rate of mortality for elderly patients after fracture of the hip in the 1980s. *J Bone Joint Surg Am* 1987, **69**: 1335–1340

9 Lavernia CJ. Hemiarthroplasty in hip fracture care: effects of surgical volume on short-term outcome. *J Arthroplasty* 1998; **13**: 774–8

10 Hamilton BH, Ho V. Does practice make perfect? Examining the relationship between hospital surgical volume and outcomes for hip fracture patients in Quebec. *Med Care* 1998; **36**: 892–903

11 Taylor DH Jr, Whellan DJ, Sloan FA. Effects of admission to a teaching hospital on the cost and quality of care for Medicare beneficiaries. *N Engl J Med* 1999; **340**: 293–9

12 Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; **91**: 8–15

13 Todd MM, Brown DL. Regional anesthesia and postoperative pain management: long-term benefits from a short-term intervention. *Anesthesiology* 1999; **91**: 1–2

14 Singelyn FJ, Deyaert M, Joris D, Pendeville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth Analg* 1998; **87**: 88–92

15 Williams-Russo P, Sharrock NE, Haas SB, *et al.* Randomized trial of epidural versus general anesthesia. Outcomes after primary total knee replacement. *Clin Orthop* 1996; **331**: 199–208

16 Ethans KD, MacKnight C. Hip fracture in the elderly. An interdisciplinary team approach to rehabilitation. *Postgrad Med* 1998; **103**: 63–4, 67–70, 157–8

17 Hamlet WP, Lieberman JR, Freedman EL, Dorey FJ, Fletcher A, Johnson EE. Influence of health status and the timing of surgery on mortality in hip fracture patients. *Am J Orthop* 1997; **26**: 621–7

British Journal of Anaesthesia 84 (2) 141–3 (2000)

BJA

Editorial II

Anaesthesia and the nitric oxide–cyclic GMP pathway in the central nervous system

Twenty years ago, the concept that a simple gas, known to anaesthetists as a toxic contaminant of nitrous oxide cylinders, was a biological mediator, was unthinkable. However, nitric oxide has roles in blood pressure regulation, neurotransmission, immunity and cardiovascular function. Nitric oxide is synthesized from L-arginine by the action of the enzyme nitric oxide synthase (NOS). There are three distinct isoforms: type I (also known as 'neuronal') NOS; type II ('inducible') NOS; and type III ('endothelial constitutive') NOS. It is now clear that many cells can generate nitric oxide, and many cells express more than one isoform of the enzyme.

NOS enzymes are cytochrome P450-like haem proteins with binding sites for calmodulin, NADPH, flavine adenine dinucleotide (FAD) and flavine mononucleotide (FMN), and a requirement for tetrahydrobiopterin for catalytic activity. Tetrahydrobiopterin is a member of the pterin family and is synthesized in many cells. GTP cyclohydrolase I is the first enzyme in its synthesis and is upregulated in response to the same stimuli which regulate NOS synthesis. Each NOS enzyme catalyses the five electron oxidation of L-arginine to generate nitric oxide, with citrulline as a byproduct. Type I NOS is the predominant isoform in the central nervous system. It is constitutively expressed but requires stimulation of the calcium–calmodulin pathway for activation, through increased intracellular calcium. The synthesis and release of nitric oxide by type I NOS is rapid and independent of *de novo* protein synthesis.

The primary way in which nitric oxide mediates cellular and intercellular communication is through activation of soluble guanylyl cyclase resulting in cGMP formation and activation of downstream signalling pathways. Both excitatory and inhibitory neurotransmitter pathways are implicated in the state of anaesthesia and the nitric oxide pathway has also been shown to be a component.[1]

Depending on location, NOS activation in the central nervous system is coupled to one of two types of physiological stimuli. postsynaptic neurotransmitter receptor stimulation leading to calcium influx, or action potentials in presynaptic nerves resulting in calcium influx through voltage-sensitive calcium channels[2] Postsynaptically, activation of glutamate receptors has been shown to result in increases in cGMP, and is attenuated by NOS inhibitors and NMDA receptor antagonists.[3]

Type I NOS in the brain is apparently associated almost exclusively with neurones[4] and co-localized with argininosuccinate synthase, the enzyme involved in the metabolic conversion of citrulline to arginine. The distribution of nitric oxide producing cells and those that accumulate cGMP are usually distinct, supporting the concept of a role for nitric oxide as an inter-neuronal messenger.[5] cGMP and cGMP-dependent kinases are also detectable in the spinal cord.[6,7]

Nitric oxide release in response to anaesthesia has been assessed *in vitro* in terms of nitric oxide itself, measured as its breakdown products, nitrite and nitrate; as ^{14}C-citrulline from ^{14}C-arginine, by conversion of oxy- to met-haemoglobin; or by chemiluminescence or electrochemical detection. In addition, cGMP release has been used as an index of nitric oxide production. *In vivo* studies are limited, but the use of microdialysis probes directly in the brains of rats to measure either nitrite–nitrate[8,9] or cGMP[10] has been described. The study by Wu and colleagues in this issue[11] used such a technique, coupled with measurement of nitrite after reduction of nitrate using a cadmium-coated column and reaction with an azo dye to measure the effect of ketamine anaesthesia on nitric oxide release.

A direct inhibitory effect of halothane and isoflurane[12] on NOS activity in rat brain homogenates has been described. However, another study found no effect of halothane, isoflurane or enflurane on the activity of partially purified rat brain NOS.[13] Ketamine and pentobarbital had no effect on rat brain NOS activity in one study,[12] whereas ketamine, thiopental and midazolam inhibited NOS activity in a rat brain preparation.[14] Different techniques were used in these *in vitro* studies and it is unclear if measurement of nitric oxide production from brain homogenates in an artificial *in vitro* situation provides a clear insight into the effects *in vivo*.

There have also been conflicting results from studies investigating the effect of anaesthetics on cGMP in the central nervous system. *In vitro*, halothane attenuated NMDA-mediated accumulation of cGMP, but not cGMP from exogenous nitric oxide donors, in studies using rat cerebellar slices.[15] Isoflurane also suppressed NMDA-stimulated cGMP but not that from nitroprusside stimulation. In contrast, thiopental suppressed cGMP release regardless of the stimulant. These authors suggested that potent inhalation agents inactivate either NOS or its co-factors, and that thiopental suppresses guanylate cyclase activity.[15] However, in cultured fetal rat cortical neurones, it was found that isoflurane, in contrast, potentiated cGMP release in response to glutamatergic agonists but enflurane and halothane had no effect.[16]

There is an inverse correlation between cerebellar cGMP and P_{CO_2},[17] illustrating the need to maintain arterial blood-gas values during *in vivo* studies. It is not clear if this is a

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

direct effect on cGMP, although prolonged hypoxia increases cerebellar nitric oxide formation through upregulation of GTP cyclohydrolase I expression, which is the first enzyme in the pathway of tetrahydrobiopterin synthesis.[18] In the study by Wu and colleagues, animals did not undergo ventilation and it is not known if normocapnia was maintained.[11]

There are several older reports which describe the effects of various drugs on cGMP in the brains of rats and mice. In pentobarbital and halothane anaesthetized animals, cGMP decreased in most brain regions studied.[19] Benzodiazepines, morphine, sodium barbital and haloperidol also decreased cGMP.[20–23] However, these changes in cGMP were attributed to altered motor function as a result of anaesthesia or sedation, as paralysis for even short periods of time also resulted in decreased cGMP.[24] In addition, increased locomotor activity induced by agents which caused tremors and seizures[25] or forced running[26] resulted in an increase in cGMP.

In rat cerebellar slices, ketamine depressed NMDA or glutamate stimulated cGMP but not non-receptor mediated cGMP.[27] These *in vitro* studies are in contrast with the findings of increased *in vivo* nitric oxide production in response to the NMDA receptor antagonist ketamine, reported by Wu and colleagues.[11] It might be expected that ketamine would decrease cGMP by blocking NMDA receptor-mediated NOS activation. However, acetylcholine does not activate NOS via NMDA receptors, yet acetylcholine stimulated-cGMP was reduced by ketamine in a study using rat thoracic aorta.[28] Although other *in vitro* studies have shown decreased cGMP in response to ketamine after NDMA, quisqualate or glutamate treatment of cultured cerebral neurones, closer examination of the data reveal that ketamine did not decrease endogenous, unstimulated basal cGMP production.[29] It is also worth noting that stimulation of neurones with kainate, which is a selective ionotropic agonist similar to NMDA, and which also increases intracellular calcium, was unaffected by ketamine.[29] Other glutamate receptor antagonists had neither basal nor stimulated effects on cGMP. The study by Wu and colleagues[11] investigated the effect of ketamine on unstimulated nitric oxide release. Alterations in calcium mobilization or inositol triphosphate are unlikely as these have been shown to be unaffected by ketamine in studies using cultured vascular smooth muscle cells. Glutamate uptake into cultured rat synaptosomes is also unaltered by ketamine. The concentration of ketamine used in *in vitro* studies is also relevant. Many studies have used concentrations above those encountered clinically in the circulation during ketamine anaesthesia, and local concentrations in the brain are not known. In addition, it should be appreciated that changes in nitric oxide release may not necessarily be reflected by changes in cGMP.

Type I NOS knockout mice show no difference in minimum alveolar concentration for isoflurane, with no effect of NOS inhibitors, although inhibitors in normal mice reduce MAC, thus revealing a compensatory mechanism for the absence of type I NOS.[30] As another example, the increase in cerebral blood flow which occurs in response to hypercapnia is nitric oxide-dependent and is blocked by NOS inhibitors. However, hypercapnic cerebral blood flow responses remain intact in type I knockout mice, and NOS inhibitors do not block the response.[31] This shows that the hypercapnic blood flow response in these animals is not caused by upregulation of other NOS isoforms but is mediated by an alternative, nitric oxide-independent mechanism. Compensation by alternative pathways appears to be a common physiological reaction to deficits in nitric oxide biosynthesis and has been observed in several systems.

These findings and the interesting results presented by Wu and colleagues,[11] coupled with the discrepancies in previous studies, dictate that further work is required to elucidate the complex relationship between anaesthesia and the nitric oxide pathway.

H. F. Galley
Academic Unit of Anaesthesia and Intensive Care
University of Aberdeen
Aberdeen AB25 2ZD, UK

References

1 Johns RA. Nitric oxide, cyclic GMP and the anaesthetic state. *Anesthesiology* 1996; **85**: 457–9

2 Garthwaite J, Boulton CL. Nitric oxide signalling in the central nervous system. *Annu Rev Physiol* 1995; **57**: 683–706

3 East SJ, Garthwaite J. NMDA receptor activation in rat hippocampus induces cyclic GMP formation through the L-arginine–nitric oxide pathway. *Neurosci Lett* 1991; **123**: 17–9

4 Bredt DS, Hwang PM, Snyder SH. Localization of nitric oxide synthase indicating a neural role for nitric oxide. *Nature* 1990; **347**: 768–70

5 Southam E, Garthwaite J. Nitric oxide–cyclic GMP pathway in rat brain. *Neuropharmacology* 1993, **32**: 1267–77

6 Bhargava HN, Cao YJ. Effect of chronic administration of morphine, U-50, 488H and [D-Pen2,D-Pen5] enkephalin on the concentration of cGMP in brain regions and spinal cord of the mouse. *Peptides* 1997; **18**: 1629–34

7 Qian Y, Chao DS, Santillano DR, *et al.* cGMP-dependent protein kinase in dorsal root ganglion: relationship with nitric oxide synthase and nociceptive neurons. *J Neurosci* 1996; **16**: 3130–8

8 Luo D, Knezevich S, Vincent SR. N-methyl-D-aspartate-induced nitric oxide release: an *in vivo* microdialysis study. *Neuroscience* 1993; **57**: 897–900

9 Luo D, Vincent SR. NMDA-dependent nitric oxide release in the hippocampus *in vivo*: interactions with noradrenaline. *Neuropharmacology* 1994, **33**: 1345–50

10 Luo D, Leung E, Vincent R. Nitric oxide-dependent efflux of cGMP in rat cerebellar cortex: an *in vivo* microdialysis study. *J Neurosci* 1994; **14**: 263–71

11 Wu J, Kikuchi T, Wang Y, Sato K, Okumura F. NOX– concentrations in the rat hippocampus and striatum have no direct relationship to anaesthesia induced by ketamine. *Br J Anaesth* 2000; **84**: 183–9

12 Tobin JR, Martin LD, Breslow MJ, Traystman RJ. Selective inhibition of brain nitric oxide synthase. *Anesthesiology* 1994; **81**· 1264–9

13 Rengasamy A, Pajewski TN, Johns RA. Inhalational anaesthetic

effects on rat cerebellar nitric oxide and cyclic guanosine monophosphate production. *Anesthesiology* 1997; **86**: 689–98

14 Galley HF, Webster NR Brain nitric oxide synthase activity is decreased by intravenous anaesthetics. *Anesth Analg* 1996; **83**: 591–4

15 Terasako K, Nakamura K, Miyawaki I, Toda H, Kakuyama M, Mori K. Inhibitory effects of anaesthetics on cyclic GMP accumulation in rat cerebellar slices. *Anesth Analg* 1994; **79**. 921–6

16 Loeb AL, Gonzales JM, Reichard PS. Isoflurane enhances glutamatergic agonist stimulated nitric oxide synthesis in cultured neurons. *Brain Res* 1996; **734**: 295–300

17 Mueller RA, Lundberg D, Frye GD, Mailman RB, Bresse GR. Cerebellar cGMP varies with motor function and respiratory exchange. *Neurosci Lett* 1978; **10**: 89–92

18 Guo Y, Ward ME, Beasjours S, Mori M, Hussain SN. Regulation of cerebellar nitric oxide production in response to prolonged *in vivo* hypoxia. *J Neurosci Res* 1997; **49**: 89–97

19 Kant GJ, Muller TW, Lenox RH, Meyerhoff JL. *In vivo* effects of pentobarbital and halothane anaesthesia on levels of adenosine 3′,5′-monophosphate and guanosine 3′,5′-monophosphate in rat brain regions and pituitary. *Biochem Pharmacol* 1980; **29**: 1891–6

20 Mao CC, Guidotti A, Costa E. Inhibition by diazepam of the tremor and increase in cGMP elicited by harmaline. *Brain Res* 1975, **83**: 516–19

21 Biggio G, Guidotti A, Costa E. On the mechanism of the decrease in cerebellar cyclic GMP content elicited by opiate receptor agonists. *Arch Pharmacol* 1977; **296**: 117–21

22 Biggio G, Corda MG, Casu M, Gessa GL. Effect of chronic treatment with neuroleptics on the content of 3′,5′-cyclic guanosine monophosphate in cerebellar cortex of rats. *Life Sci* 1978; **23**: 649–52

23 Lenox RH, Wray HL, Kant GJ, Hawkins TD, Meyerhoff JL. Changes in brain levels of cyclic nucleotides and γ-aminobutyric acid in barbiturate dependence and withdrawal. *Eur J Pharmacol* 1979, **55**: 159–69

24 Lundberg DBA, Breese GR, Mailman RB, Frye GD, Mueller RA. Depression of some drug-induced *in vivo* changes of cerebellar guanosine 3′,5′-monophosphate by control of motor and respiratory responses. *Mol Pharmacol* 1979; **15**: 246–56

25 Vulliemoz Y, Verosky M, Alpert M, Triner L. Effect of enflurane on cerebellar cGMP and on motor activity in the mouse. *Br J Anaesth* 1983; **55**: 79–84

26 Kant GJ, Meyerhoff JL, Bunnell BN, Lenox RH. Cyclic AMP and cyclic GMP response to stress in brain and pituitary: stress elevates pituitary cyclic AMP. *Pharmacol Biochem Behav* 1982, **17**. 1067–72

27 Miyawaki I, Nakamura K, Yokubol B, Kitamura R, Mori K. Suppression of cGMP formation in rat cerebellar slices by propofol, ketamine and midazolam. *Can J Anaesth* 1997; **44**: 1301–7

28 Miyawaki I, Nakamura K, Terasako K, Toda H, Kakuyama M, Mori K. Modification of endothelium dependent relaxation by propofol, ketamine and midazolam. *Anesth Analg* 1995, **81** 474–9

29 Gonzales JM, Loeb AL, Reichard PS, Irvine S. Ketamine inhibits glutamate-, N-methyl-D-aspartate-, and quisqualate-stimulated cGMP production in cultured cerebral neurons. *Anesthesiology* 1995, **82**: 205–13

30 Ichinose F, Huang PL, Zapol WM. Effects of targeted neuronal nitric oxide synthase gene disruption and nitro^{G}-L-arginine methylester on the threshold for isoflurane anesthesia. *Anesthesiology* 1995; **83**: 101–8

31 Irikura K, Huang PL, Ma WS, *et al* Cerebrovascular alterations in mice lacking neuronal nitric oxide synthase gene expression *Proc Natl Acad Sci USA* 1995; **92**: 6823–7

British Journal of Anaesthesia 84 (2): 144–50 (2000)

BJA

CLINICAL INVESTIGATIONS

Effect of continuous epidural 0.2% ropivacaine *vs* 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after abdominal hysterectomy

H. Jørgensen*, J. S. Fomsgaard, J. Dirks, J. Wetterslev and J. B. Dahl

Department of Anaesthesiology and Intensive Care, Herlev University Hospital, Copenhagen County, 2730 Herlev, Denmark

**Corresponding author*

We have investigated the effect of 24-h postoperative continuous epidural infusion of 0.2% ropivacaine or 0.2% bupivacaine 8 ml h^{-1} on pain, request for supplementary analgesics, motor block and gastrointestinal function, in a double-blind, randomized study in 60 patients undergoing open hysterectomy. There were no significant differences between groups in pain, number of patients requesting supplementary analgesics, motor block, ability to walk or time to first flatus or stool. In the subgroup of patients who received supplementary analgesics, patients in the ropivacaine group received significantly more ketorolac than patients in the bupivacaine group. Time to discharge from hospital was similar with ropivacaine and bupivacaine.

Br J Anaesth 2000; **84**: 144–50

Keywords: anaesthetic techniques, epidural; anaesthetics local, bupivacaine; anaesthetics local, ropivacaine; pain, postoperative; surgery, gynaecological

Accepted for publication: August 24, 1999

Experimental and clinical studies have demonstrated that ropivacaine has comparable pharmacodynamic and pharmacokinetic properties to bupivacaine,[1–3] but less cardiac and central nervous system toxicity.[4] Furthermore, it has been claimed that ropivacaine produces less motor block but equivalent analgesia compared with bupivacaine in similar doses,[5–8] although this is controversial.[9 10] Only one study has compared continuous epidural ropivacaine and bupivacaine in equal concentrations and doses for postoperative pain relief.[11] In this study, postoperative pain scores after total knee arthroplasty were slightly, but significantly, higher in patients receiving 0.2% ropivacaine compared with 0.2% bupivacaine administered in a lumbar epidural catheter. Postoperative morphine consumption was not significantly different, whereas motor block, evaluated using a modified Bromage score, was significantly less with ropivacaine.[11] Comparisons of the effects of similar doses of ropivacaine and bupivacaine on postoperative pain and motor function after abdominal surgery have not been reported.

The aim of this study was to investigate the effect of continuous thoracic epidural 0.2% ropivacaine *vs* 0.2% bupivacaine on postoperative pain, motor block and gastrointestinal function after hysterectomy.

Patients and methods

We studied 60 patients, aged 18–75 yr, undergoing elective abdominal total or supravaginal hysterectomy through a Pfannenstiel or inferior median incision. Informed written consent was obtained from all patients and approval was obtained from the Local Ethics Committee and the Danish National Board of Health. Patients were recruited from the Department of Gynaecology, Herlev University Hospital, during the period October 1997 to December 1998. Patients were not included if they were unable to cooperate, had a body weight ≥(1.3×body height (cm)–100), had moderate to severe heart or lung disease (ASA ≥III), a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, or had contraindications to insertion of an epidural catheter.

The study was double-blind and randomized. The study drugs, 0.2% ropivacaine (molar concentration of the base 0.0061 mol litre^{-1}) or 0.2% bupivacaine (molar concentration of the base 0.0058 mol litre^{-1}), were prepared by the manufacturer (Astra Pain Control, Södertalje, Sweden) in identical containers, marked with the name of the project, the investigator's name and consecutive patient numbers.

One hour before surgery, patients received sublingual

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

triazolam 0.125 mg. Before induction of general anaesthesia, an 18-gauge epidural catheter was inserted via a Touhy needle and advanced 4–5 cm into the epidural space at the T10–11 level, and a 4-ml test dose of 2% lidocaine with epinephrine was administered. A bolus dose of 16 ml of 2% lidocaine with epinephrine was administered, followed by continuous infusion of 8 ml h^{-1} of 2% lidocaine throughout the operation, using a Pharmacia Deltec pump (in one patient aged 74 yr and of small constitution, a reduced bolus dose of 2% lidocaine 10 ml was administered).

General anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1} and alfentanil 1.0 mg, and a laryngeal mask airway was inserted. Propofol without nitrous oxide was given for maintenance of anaesthesia. No additional doses of lidocaine or alfentanil were administered. Hypotension was treated with i.v. infusion of isotonic sodium chloride, 6% HAES or ephedrine 5 mg i.v. in incremental doses, when systolic arterial pressure was less than 90 mm Hg. Fluid and blood losses were replaced according to the requirements of the department.

Postoperative analgesia and antiemetics

At skin closure, patients were allocated randomly to receive an epidural bolus dose of either 0.2% ropivacaine or 0.2% bupivacaine 8 ml, followed by a continuous epidural infusion of 0.2% ropivacaine or 0.2% bupivacaine 8 ml h^{-1} for 24 h. For the first 48 h after surgery, all patients received paracetamol 2 g rectally every 6 h. For the first 0–72 h after surgery, ketorolac 30 mg i.m. was administered with a minimum of 6-h intervals on demand from patients. If additional analgesia was required before another dose of ketorolac could be administered, morphine 0.125 mg kg^{-1} i.m. was given.

Patients were given ondansetron 4 mg i.v. with a lockout period of 8 h if they demanded an antiemetic. If additional antiemetic was required before another dose of ondansetron could be administered, metoclopramide 10 mg i.v. was given.

Postoperative recordings and pain assessments

Before operation, all patients were instructed on the use of the visual analogue scale (VAS) pain score, and to request supplementary analgesics and antiemetics if needed.

Pain scores on a visual analogue scale (VAS, 0 mm=no pain, 100=worst pain imaginable) at rest, on coughing and on mobilization from the supine to the sitting position were assessed by the patients at 4, 6, 22, 24, 26, 30, 48 and 72 h after operation. The number of ketorolac and morphine doses was recorded at the same times. Levels of sensory block to pinprick bilaterally were assessed at 6, 24, 26 and 30 h after operation; in the event of asymmetrical block, the smaller spread was recorded. Motor block was assessed using a four-point modified Bromage scale (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, 3=inability to flex ankle joints) at 6, 22, 24, 26 and 30 h after operation. Ability to walk on the floor (0=no difficulty, 1=little difficulty, 2=very difficult, 3=impossible, 4=difficult or impossible for reasons other than motor block) was assessed at 6, 22, 24, 26, 30 and 48 h after operation. At all visits, gastrointestinal function was monitored by asking patients if and when they had their first flatus and stool, and if they had experienced nausea (0=no, 1=light, 2=moderate, 3=severe) and/or vomiting since the last assessment.

Calculation of sample size and statistical analysis

The primary end-points of this study were pain during mobilization and motor block at 24 h after operation. Calculation of sample size was based on the following variables: type 1 error 5%; type 2 error 20%; and minimal difference not to be overlooked: 35% fewer patients with motor block (Bromage >0) in the ropivacaine group. The sample size needed to demonstrate this difference was 29 in each group.

Data are presented as median (upper and lower quartiles). Statistical analyses were performed using the Mann–Whitney rank sum test for unpaired data, the Wilcoxon signed rank sum test for paired data and Fisher's exact test for dichotomous data, where appropriate. If multiple testing was performed, significant *P* values were corrected with a Bonferroni factor for multiple comparisons. $P<0.05$ was considered statistically significant. Calculations were performed using SPSS 8.0 for Windows.

Results

We considered 114 consecutive patients for inclusion in the study. Fifty-four patients were excluded: two were aged more than 75 yr; seven were unable to communicate properly; 15 were adipose; five had moderate to severe heart or lung diseases; seven used analgesics, steroid hormones or suffered alcohol–drug abuse; six had a hysterectomy in addition to other surgical procedures; seven needed anaesthetic procedures other than those allowed in the protocol; three did not want to participate; and two patients were not included because of lack of time. Thus 60 patients were included in the study, but nine of these were excluded during the 72 h study period: five immediately after operation (three because of haemorrhage, one because of the surgical approach and one because of displacement of the epidural catheter); two at 24 h (one because of haemorrhage and reoperation and one because of withdrawal of consent); and two at 48 h (one because of withdrawal of consent and one because of discharge from hospital before 48 h). Of the nine excluded patients, three had received ropivacaine and six bupivacaine.

There were no significant differences between groups for patient characteristics or operative data (Table 1). In particular, intraoperative hypotension was not a clinical problem, and only 12 patients in each group needed i.v. ephedrine. Fluid replacements and ephedrine use are shown in Table 1.

Table 1 Patient and perioperative data (median (range) or number)

	Group	
	Ropivacaine	Bupivacaine
No of patients at the end of surgery	28	27
No of patients 24 h after surgery	28	25
No of patients 48–72 h after surgery	27	24
Age (yr)	48 (36–75)	47 (34–72)
Weight (kg)	71 (50–85)	63 (52–80)
Height (cm)	166 (154–180)	168 (156–173)
ASA (I/II)	19/9	16/11
Pfannenstiel/inferior median incision	20/8	17/8
Duration of surgery (min)	80 (60–127)	80 (44–195)
Perioperative haemorrhage (ml)	200 (100–2200)	250 (100–2800)
Perioperative sodium chloride (ml)	1400 (1000–2200)	1300 (500–2700)
Perioperative 6% HAES (ml)	500 (450–1500)	500 (0–1500)
Perioperative ephedrine (mg)	0 (0–20)	0 (0–10)

Table 2 Number of patients who requested ketorolac. ns=Not significant

	Group		*P*
Postoperative period	Ropivacaine	Bupivacaine	
0–24 h			
No. of patients receiving ketorolac	20/28	19/25	ns
No. of doses in patients receiving ketorolac	40	24	0 018
24–48 h			
No of patients receiving ketorolac	19/27	14/24	ns
No. of doses in patients receiving ketorolac	45	31	ns
48–72 h			
No. of patients receiving ketorolac	7/27	1/24	ns
No of doses in patients receiving ketorolac	7	2	ns

Table 3 Number of patients who requested morphine. ns=Not significant

	Group		*P*
Postoperative period	Ropivacaine	Bupivacaine	
0–24 h			
No. of patients receiving morphine	17/28	16/25	ns
No. of doses in patients receiving morphine	46	24	ns
24–48 h			
No of patients receiving morphine	9/27	11/24	ns
No. of doses in patients receiving morphine	15	19	ns
48–72 h			
No of patients receiving morphine	3/27	1/24	ns
No of doses in patients receiving morphine	5	2	ns

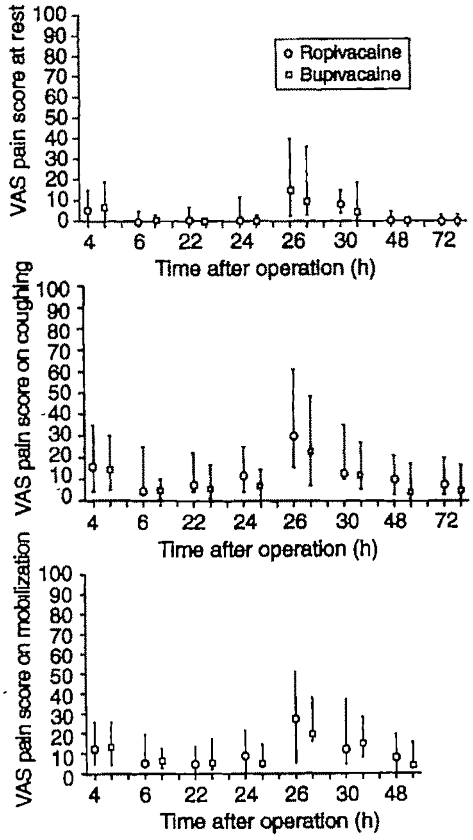


Fig 1 Median (upper and lower quartiles) visual analogue scale (VAS) pain scores at rest, on coughing and on mobilization from the supine to the sitting position. No significant differences between groups.

There were no significant differences between groups for VAS scores at rest, during cough or during mobilization from the supine to the sitting position at any time (ns) (Fig. 1). VAS scores in both groups at rest, during cough and during mobilization increased significantly from 24 h to 26 h after operation, after the epidural catheters had been removed ($P<0.0001$).

There were no significant differences in the number of patients requesting supplementary ketorolac (Table 2) or morphine (Table 3) between groups at 0–24 h, 24–48 h or 48–72 h after operation. However, in the subgroup of patients who received supplementary analgesics at 0–24 h after operation, those in the ropivacaine group received significantly more ketorolac than those in the bupivacaine group ($P=0.018$, after Bonferroni correction for six comparisons).

There were no differences in the spread of sensory block between groups, except at 26 h after operation where patients in the ropivacaine group had a smaller spread than those in the bupivacaine group ($P=0.042$, after Bonferroni correction for six comparisons).

There was no significant difference in motor block, assessed by the modified Bromage scale, at any assessment (Fig. 2). Nine of 28 (32%) patients in the ropivacaine group compared with 11 of 27 (41%) in the bupivacaine group ($P=0.70$), and 21 of 28 (75%) in the ropivacaine group compared with 15 of 25 (60%) in the bupivacaine group ($P=0.38$) were able to walk on the floor without difficulty at 6 h and 24 h after operation, respectively (Fig. 3). At 24 h after operation, ability to walk on the floor could not be evaluated in six patients in the ropivacaine group and in one patient in the bupivacaine group for reasons other than motor block. In the ropivacaine group,

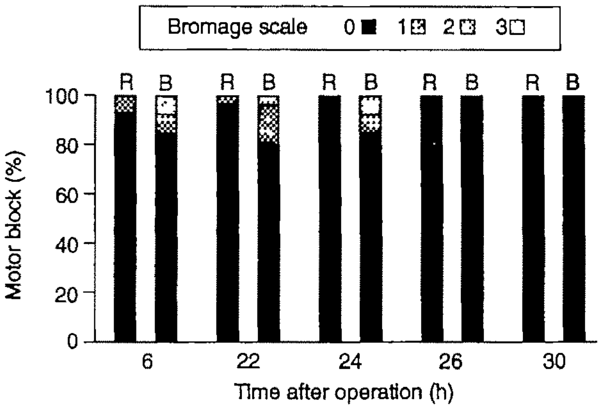


Fig 2 Motor block, assessed using the modified Bromage scale 0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees and 3=inability to flex ankle joints. Columns show percentages of patients with a particular Bromage score in the ropivacaine (R) and bupivacaine (B) groups at 6, 22, 24, 26 and 30 h after operation. No significant differences between groups

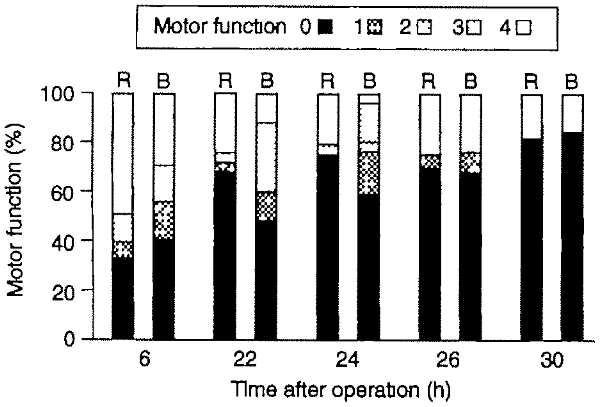


Fig 3 Motor function, assessed by walking on the floor 0=no difficulty, 1=little difficulty, 2=very difficult, 3=impossible, 4=difficult or impossible for reasons other than motor block Columns show percentages of patients with a particular score in the ropivacaine (R) and bupivacaine (B) groups at 6, 22, 24, 26 and 30 h after operation. No significant differences between groups

Table 4 Percentage of patients with light to severe nausea and percentage who vomited since the last assessment in the ropivacaine and bupivacaine groups

	Time after operation (h)							
	0–4	**4–6**	**6–22**	**22–24**	**24–26**	**26–30**	**30–48**	**48–72**
Light to severe nausea								
Ropivacaine	36	29	39	21	21	25	22	15
Bupivacaine	33	15	35	16	8	23	17	22
Vomited since last assessment								
Ropivacaine	4	18	32	11	7	18	7	0
Bupivacaine	11	15	27	0	8	12	8	0

Table 5 Number of patients who requested antiemetics (ondansetron or metoclopramide)

Postoperative period	**Ropivacaine**	**Bupivacaine**
0–24 h		
No of patients receiving antiemetics	14/28	10/25
No of doses in patients receiving antiemetics	26	14
24–48 h		
No of patients receiving antiemetics	3/27	4/24
No of doses in patients receiving antiemetics	5	4
48–72 h		
No. of patients receiving antiemetics	1/27	0/24
No of doses in patients receiving antiemetics	2	0

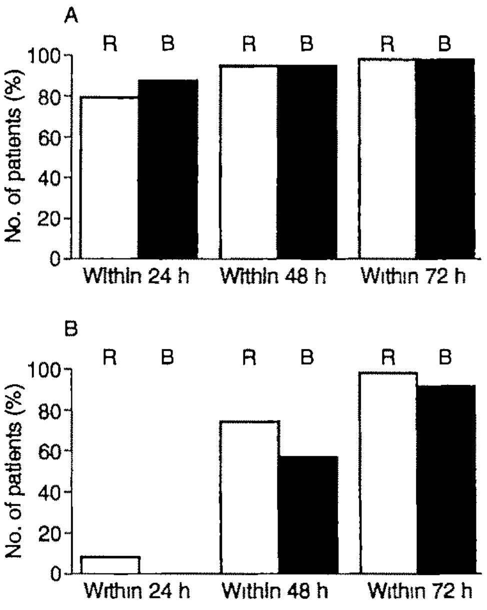


Fig 4 Cumulative percentage of patients with first flatus (A) and first stool (B) in the ropivacaine (R) and bupivacaine (B) groups within 24, 48 and 72 h after operation. No significant differences between groups

this was because of dizziness in five patients and pain in one. In the bupivacaine group, one patient could not be evaluated because of fatigue.

The two groups had a similar incidence of nausea (ns) and vomiting (ns) (Table 4). There were no significant differences in the number of patients requesting antiemetics or the number of doses between groups at 0–24 h, 24–48 h and 48–72 h after operation (ns) (Table 5). Side effects were of a mild nature in most patients, except for six (three in the ropivacaine and three in the bupivacaine group) who experienced severe nausea. There was no difference in time to first flatus (Fig. 4A) or time to first stool (Fig. 4B). Most patients had an indwelling bladder catheter which was removed on the morning after surgery. After removal, two patients, both from the bupivacaine group, complained of urinary retention. There was no difference in time to discharge from hospital between groups (bupivacaine median 4 (quartiles 3–5) days, ropivacaine 4 (4–5) days (ns).

Discussion

The aim of postoperative analgesia is to provide subjective comfort with minimum side effects, and to blunt autonomic and somatic reflex responses to pain, to allow early ambulation and restoration of function.

A large number of patients experienced moderate to severe pain after open hysterectomy, and pain scores of 40–60 mm on a 100-mm VAS scale are not unusual.[12–14] Furthermore, hysterectomy is often associated with considerable nausea and vomiting.[15–18] Postoperative gastrointestinal paralysis may last for 2–5 days, depending on the technique provided for anaesthesia and postoperative analgesia.[18–20] In a pilot study conducted in our department, 30 patients undergoing open hysterectomy under general anaesthesia with isoflurane or sevoflurane, followed by postoperative pain treatment with paracetamol and systemic morphine, had median VAS scores during coughing of 48, 40 and 30 mm at 4, 24 and 48 h after surgery, respectively. Seventy-two hours after operation only 83% and 20% of patients had experienced their first flatus and stool, respectively (unpublished observations).

Epidural analgesia with local anaesthetics after lower abdominal surgery is a powerful method of relieving postoperative pain, provided that the catheter is placed at the correct dermatome.[21] In addition, epidural local anaesthetics may reduce gastrointestinal paralysis and postoperative nausea and vomiting by inhibition of visceral reflex activity and reduced need for perioperative opioids.[18–20 22]

The problem of persistent motor block limits the usefulness of epidural infusions with local anaesthetics. Although controversial, it has been claimed that ropivacaine produces comparable sensory, but less intense, motor block compared with bupivacaine.[11 23 24] This has not been investigated in patients undergoing lower abdominal surgery.

The effect of continuous epidural infusion with ropivacaine on postoperative pain, analgesic requirements and motor function has been investigated in several studies.[25–30] A dose-finding study with 0.1%, 0.2% and 0.3% ropivacaine by Scott and colleagues in patients undergoing lower abdominal surgery demonstrated that 0.2% ropivacaine 10 ml h^{-1} provided the best balance between analgesia and motor block.[29] In another study, Etches and colleagues investigated the effect of epidural 0.2% ropivacaine at a rate of 6, 8, 10, 12 or 14 ml h^{-1} after lower abdominal surgery. They found that ropivacaine 10–14 ml h^{-1} (but not 6 or 8 ml h^{-1}) reduced PCA morphine requirements but had little effect on pain scores. Significant motor block was observed in at least 30% of patients receiving ropivacaine 8–14 ml h^{-1}.[30] The majority of patients in this study had a lumbar epidural catheter, however, and no information was provided about the nature of the surgical procedures.[30]

Bupivacaine is known to provide a more intense and longer lasting surgical block than ropivacaine in similar doses and concentrations.[7 31 32] Furthermore, we aimed to mobilize patients as soon as possible after surgery. Consequently, 2% lidocaine was chosen for intraoperative analgesia in all patients to standardize and reduce the duration of postoperative residual motor block, resulting from intraoperative analgesia. Intra- and postoperative administration of opioids was restricted and standardized to reduce PONV and gastrointestinal paralysis. Thus paracetamol was given to all patients, and ketorolac was chosen as the first-choice escape analgesic. Morphine was administered after operation only if ketorolac was insufficient.

Given these premises, we observed no differences in pain intensity at rest, or during coughing and ambulation between groups who received ropivacaine or bupivacaine at any time.

Both regimens were effective, and most patients had pain scores less than 30 mm even during cough and mobilization. Epidural infusions of ropivacaine and bupivacaine contributed significantly to analgesia, as pain scores increased in both study groups immediately after withdrawal of the epidural catheters.

Significantly more doses of ketorolac were administered to patients who requested supplementary analgesics in the ropivacaine group, and this may indicate that ropivacaine is less effective for analgesia. Furthermore, there was a trend towards request for more supplementary morphine (P=0.04, not corrected with Bonferroni factor) in the ropivacaine group compared with the bupivacaine group. This trend was not reflected in the frequency of postoperative nausea and vomiting or gastrointestinal function, which was similar in both groups, and thus may seem clinically irrelevant. Gastrointestinal function, evaluated by time to first flatus and first stool, was restored in most patients within 48 h after surgery. These findings are in agreement with the results of previous studies.[19 22]

Evaluated using the modified Bromage score, 7% of patients who received ropivacaine suffered from motor block (Bromage score >0) at 6 h after operation compared with 15% in the bupivacaine group. At 24 h after operation, corresponding values were 0% and 16%, respectively. These differences were not statistically significant. Calculation of sample size in our study was based on a previous report concerning orthopaedic surgery, where 12% of patients who received 0.2% ropivacaine had motor block compared with 44% who received bupivacaine 24 h after surgery.[11] To demonstrate a significant difference in motor block of 16% at the 5% level, as observed in our study, 246 patients should have been included. However, as emphasized previously,[30 33] the Bromage score may not necessarily reflect the desired outcome of mobilization. At 6 h after operation, 68% of patients in the ropivacaine group compared with 60% in the bupivacaine group were unable to walk on the floor without difficulty. In 18% and 30% of patients, this was caused by motor impairment, whereas 50% and 30% were unable to walk because of other reasons, most often dizziness, in the ropivacaine and bupivacaine groups, respectively. At 24 h after operation, 25% of patients in the ropivacaine group *vs* 40% in the bupivacaine group were unable to walk, and these values were reduced to 19% and 16%, 6 h after withdrawal of the epidural catheter where no patient had Bromage scores >0. These observations emphasize that factors other than motor block are important for early postoperative mobilization. The trend towards reduced motor block together with a significantly increased need for supplementary analgesics with ropivacaine compared with bupivacaine in similar doses and concentrations, confirm findings from a recent study in orthopaedic surgery.[11] However, these results do not support the notion that ropivacaine may have a clinically important differential sensory–motor block profile compared with bupivacaine when used for continuous epidural analgesia.

In summary, there were no significant differences between continuous epidural (T10–11) infusion of 0.2% ropivacaine and 0.2% bupivacaine 8 ml h^{-1} with respect to pain scores, Bromage scores or ability to walk after open hysterectomy. A significantly increased need for supplementary ketorolac, together with a trend towards request for more supplementary morphine, was observed with ropivacaine. This trend did not affect the incidence of postoperative nausea and vomiting, restoration of gastrointestinal function or time to discharge from hospital, which was similar with ropivacaine and bupivacaine.

Acknowledgement

The study was funded by a grant from Astra Pain Control AB, Sodertalje, Sweden, Oberstinde Kirsten Jensa la Cours Forskningslegat; Snedkermester Axel Wichmann og fru Else Wichmann's fond. We thank the staff of the Department of Gynaecology, Herlev University Hospital, including Dr Benny Andreasson and Dr Poul Hjortkjær Pedersen, for help and cooperation

References

1 Akerman B, Hellberg IB, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiol Scand* 1988; **32**: 571–8

2 Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. *Anesth Analg* 1988; **67**: 1047–52

3 Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. *Anesth Analg* 1988; **67**: 1053–8

4 Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

5 Morrison LM, Emanuelsson BM, McClure JH, *et al.* Efficacy and kinetics of extradural ropivacaine: comparison with bupivacaine. *Br J Anaesth* 1994; **72**: 164–9

6 Zaric D, Nydahl PA, Philipson L, Samuelsson L, Heierson A, Axelsson K. The effect of continuous lumbar epidural infusion of ropivacaine (0.1%, 0.2%, and 0.3%) and 0.25% bupivacaine on sensory and motor block in volunteers: a double-blind study. *Reg Anesth* 1996; **21**: 14–25

7 Brockway MS, Bannister J, McClure JH, McKeown D, Wildsmith JA. Comparison of extradural ropivacaine and bupivacaine. *Br J Anaesth* 1991; **66**: 31–7

8 Glise H, Abrahamsson H. Spino-vagal nonadrenergic inhibition of gastric motility elicited by abdominal nociceptive stimulation in the cat. *Scand J Gastroenterol* 1980; **15**: 665–72

9 Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. *Br J Anaesth* 1999; **82**. 371–3

10 Griffin RP, Reynolds F. Extradural anaesthesia for caesarean section: a double-blind comparison of 0.5% ropivacaine with 0.5% bupivacaine. *Br J Anaesth* 1995; **74**: 512–16

11 Muldoon T, Milligan K, Quinn P, Connolly DC, Nilsson K Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty. *Br J Anaesth* 1998; **80**. 680–1

12 Kuhn S, Cooke K, Collins M, Jones JM, Mucklow JC. Perceptions of pain relief after surgery. *BMJ* 1990; **300**: 1687–90

13 Stanley G, Appadu B, Mead M, Rowbotham DJ. Dose requirements, efficacy and side effects of morphine and pethidine delivered by patient-controlled analgesia after gynaecological surgery. *Br J Anaesth* 1996; **76**: 484–6

14 Eriksson-Mjoberg M, Svensson JO, Almkvist O, Olund A, Gustafsson LL. Extradural morphine gives better pain relief than patient-controlled i.v. morphine after hysterectomy. *Br J Anaesth* 1997; **78**: 10–16

15 Cruickshank RH, Spencer A, Ellis FR. Pretreatment with controlled-release morphine for pain after hysterectomy. *Anaesthesia* 1996; **51**: 1097–101

16 McIndoe AK, Warwick P, O'Connor M. A comparison of retrospective versus contemporaneous nausea scores with patient-controlled analgesia (see comments). *Anaesthesia* 1996; **51**: 333–7

17 Warriner CB, Knox D, Belo S, Cole C, Finegan BA, Perreault I. Prophylactic oral dolasetron mesylate reduces nausea and vomiting after abdominal hysterectomy. The Canadian Dolasetron Study Group. *Can J Anaesth* 1997; **44**: 1167–73

18 Asantila R, Eklund P, Rosenberg PH. Continuous epidural infusion of bupivacaine and morphine for postoperative analgesia after hysterectomy. *Acta Anaesthesiol Scand* 1991; **35**: 513–17

19 Wattwil M, Thoren T, Hennerdal S, Garvill JE. Epidural analgesia with bupivacaine reduces postoperative paralytic ileus after hysterectomy. *Anesth Analg* 1989; **68**: 353–8

20 Thorn SE, Wattwil M, Naslund I. Postoperative epidural morphine, but not epidural bupivacaine, delays gastric emptying on the first day after cholecystectomy. *Reg Anesth* 1992; **17**: 91–4

21 Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. *Anesthesiology* 1995; **83**: 727–37

22 Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. *Acta Anaesthesiol Scand* 1987; **31**: 161–4

23 McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76**: 300–7

24 Gautier P, De Kock M, Van Steenberge A, Miclot D, Fanard L, Hody JL. A double-blind comparison of 0.125% ropivacaine with sufentanil and 0.125% bupivacaine with sufentanil for epidural labor analgesia. *Anesthesiology* 1999; **90**: 772–8

25 Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—a dose finding study. *Anesth Analg* 1995; **81**: 982–6

26 Schug SA, Scott DA, Payne J, Mooney PH, Hagglof B. Postoperative analgesia by continuous extradural infusion of ropivacaine after upper abdominal surgery. *Br J Anaesth* 1996; **76**: 487–91

27 Badner NH, Reid D, Sullivan P, *et al* Continuous epidural infusion of ropivacaine for the prevention of postoperative pain after major orthopaedic surgery: a dose-finding study. *Can J Anaesth* 1996; **43**: 17–22

28 Turner G, Blake D, Buckland M, *et al.* Continuous extradural infusion of ropivacaine for prevention of postoperative pain after major orthopaedic surgery. *Br J Anaesth* 1996; **76**: 606–10

29 Scott DA, Emanuelsson BM, Mooney PH, Cook RJ, Junestrand C. Pharmacokinetics and efficacy of long-term epidural ropivacaine infusion for postoperative analgesia (in process citation). *Anesth Analg* 1997; **85**: 1322–30

30 Etches RC, Writer WD, Ansley D, *et al.* Continuous epidural ropivacaine 0.2% for analgesia after lower abdominal surgery. *Anesth Analg* 1997; **84**: 784–90

31 Brown DL, Carpenter RL, Thompson GE. Comparison of 0.5% ropivacaine and 0.5% bupivacaine for epidural anesthesia in patients undergoing lower-extremity surgery. *Anesthesiology* 1990; **72**: 633–6

32 Kerkkamp HE, Gielen MJ, Edstrom HH. Comparison of 0.75% ropivacaine with epinephrine and 0.75% bupivacaine with epinephrine in lumbar epidural anesthesia. *Reg Anesth* 1990; **15**. 204–7

33 Brodner G, Mertes N, van Aken H, *et al.* Epidural analgesia with local anesthetics after abdominal surgery: earlier motor recovery with 0.2% ropivacaine than 0.175% bupivacaine. *Anesth Analg* 1999; **88**: 128–33

British Journal of Anaesthesia **84** (2): 151–4 (2000)

Effect of meloxicam on postoperative pain after abdominal hysterectomy†

J. P. Thompson[1], P. Sharpe[1], S. Kiani[1] and O. Owen-Smith[2]

[1]*University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK.*
[2]*Royal Orthopaedic Hospital, Woodlands Hospital, Birmingham B31 2AP, UK*

We studied 36 patients, allocated randomly to receive meloxicam 15 mg rectally ($n=18$) or placebo suppository ($n=18$) before total abdominal hysterectomy in a double-blind study. Visual analogue scores for pain at rest ($P<0.005$), on movement ($P<0.05$) and on coughing ($P<0.05$) were significantly decreased in the meloxicam group during the first 24 h after surgery. Mean 24-h PCA morphine requirements were 33.2 (SD 16.9) mg and 38.2 (20.8) mg in the meloxicam and placebo groups, respectively (ns). There was no difference in the incidence of nausea, vomiting or sedation between groups.

Br J Anaesth 2000; **84**: 151–4

Keywords: analgesics non-opioid, meloxicam; non-steroidal anti-inflammatory drugs; analgesia, postoperative; surgery, gynaecological

Accepted for publication: September 27, 1999

The cyclo-oxygenase (COX) enzyme system, which catalyses the production of prostaglandins and other inflammatory mediators from arachidonic acid precursors, consists of two isoforms, COX-1 and COX-2.[1 2] COX-1 is produced constitutively throughout the body and is involved in the production of thromboxane A_2 (TXA_2) in platelets, prostaglandin E_2 (PGE_2) in the kidneys and prostacyclin in endothelial cells and gastric mucosa. COX-2 is expressed in only a few sites under normal conditions (e.g. brain, renal cortex, female reproductive tract and lung) where it has low basal activity. However, COX-2 production is induced in macrophages, endothelial cells and synoviocytes by inflammatory mediators, including cytokines and lipopolysaccharide.[1–4] It may also be induced in the kidney and gastrointestinal tract.[1] COX-1 activity predominates under physiological conditions whereas induced COX-2 is considered to be responsible for most of the prostaglandins produced during inflammation.[3] Inhibition of COX-1 is thought to account for the adverse gastrointestinal and renal effects of traditional non-steroidal anti-inflammatory drugs (NSAID) whereas COX-2 inhibition produces anti-inflammatory effects.[2–5]

Meloxicam (Mobic, Boehringer Ingelheim) is an NSAID with preferential activity on the COX-2 system.[1 4 5] In large-scale studies in patients with osteoarthritis, it has been claimed to cause less gastrointestinal side effects than non-selective NSAID.[6 7] Non-selective NSAID are commonly used analgesics for minor surgery and are useful adjunctive analgesics in patients undergoing major surgery, decreasing pain and morphine requirements.[8 9] However, their use in some groups of patients may be limited by adverse renal, gastrointestinal and haemostatic effects.[10] COX-2 preferential or COX-2 selective NSAID have theoretical advantages in the perioperative period, with the potential for decreased adverse effects, but there are no reports of their use in patients undergoing major surgery. Therefore, we have studied the effect of meloxicam on morphine requirements and pain after abdominal hysterectomy.

Patients and methods

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 36 ASA I–III females (aged 30–70 yr), undergoing total elective abdominal hysterectomy for non-malignant disease in a double-blind, randomized, placebo-controlled study. Criteria for exclusion were obesity (BMI >30 kg m^{-2}), chronic NSAID therapy, ASA status ≥III, malignant disease or contraindications to non-selective NSAID (e.g. peptic ulcer, asthma). Patients were allocated randomly to receive a suppository of either meloxicam 15 mg or placebo. Patients were unpremedicated and received a standardized general anaesthetic comprising induction of anaesthesia with propofol 2–3 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} to produce neuromuscular block. The trachea was intubated and the lungs ventilated to normocapnia. Anaesthesia was maintained with 1–2% isoflurane and 67% nitrous oxide in oxygen. The study medication (meloxicam 15 mg or placebo suppository) was administered after induction of anaesthesia

---

†Presented in part at the 7th Annual Congress of the European Society of Anaesthesiologists, May–June 1999

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Mean (SD) cumulative PCA morphine consumption (mg), incidence of nausea and sedation scores >1 during the first 24 h after surgery in the meloxicam and placebo groups

	Morphine consumption (mg)		Incidence of nausea (*n*)		Sedation score >1 (*n*)	
Time after surgery (h)	**Placebo**	**Meloxicam**	**Placebo**	**Meloxicam**	**Placebo**	**Meloxicam**
2	11.3 (5.6)	11.4 (5.5)	2	1	8	6
4	16.3 (8.3)	15.5 (7.8)	2	0	5	4
8	21.9 (13.0)	20.2 (10.1)	4	2	4	2
12	27.4 (14.9)	24.6 (12.4)	1	4	2	1
24	38.2 (20.8)	33.2 (16.9)	2	1	1	0

and before the start of surgery. Morphine 0.15 mg kg^{-1} i.v. was given to all patients at the start of surgery in a standardized manner. At the end of surgery, all patients received morphine i.v. via a standard patient-controlled analgesia (PCA) pump (1-mg bolus, 5-min lockout). Visual analogue pain scores (VAS) (0–100 mm, where 0=no pain and 100=worst pain imaginable) and PCA morphine consumption were assessed at 2, 4, 8, 12 and 24 h after surgery by nurses blinded to the study medication. VAS scores were recorded at rest, on deep inspiration and coughing, and on movement (sitting from a lying position). At these times the incidence of nausea reported on questioning and degree of sedation (scale 0–2, 0=alert, 1=drowsy but rousable to voice, 2=very drowsy, rousable to shaking) were noted. Requirements for antiemetic medication and reports of adverse effects were recorded.

Area under the curve (AUC) of the visual analogue scores for pain for 0–24 h were calculated. Mean values for AUC were compared using unpaired *t* tests. Mann–Whitney tests were used to compare non-parametric data. The morphine-sparing effect of NSAID has been estimated at 20–35%.[10] Based on previously recorded 24-h morphine requirements (mean 50.5 mg) in patients undergoing abdominal hysterectomy in our hospital, we calculated that 18 patients in each group would be required to demonstrate a 30% difference in PCA morphine consumption (16.5 mg) between groups (β=0.2, α=0.05).

Results

Mean age and weight were 43.8 (range 31–70) yr and 69.0 (SD 9.9) kg in the meloxicam group, and 40.9 (30–54) yr and 66.5 (9.1) kg in the placebo groups, respectively. Cumulative PCA morphine consumption and the incidences of nausea and sedation are shown in Table 1. Mean morphine consumption after 24 h was 33.2 (SD 16.9) mg in the meloxicam and 38.2 (20.8) mg in the placebo group (95% confidence intervals for the mean difference of 5.0 mg, −7.9 to 18.1 mg). There were no significant differences between groups at any time (ns).

Pain scores (VAS at rest, on movement and on coughing) were significantly higher in the placebo group (Fig. 1). Mean AUC pain scores at rest were 683 (354) mm h and 367 (184) mm h in the placebo and meloxicam groups, respectively (P<0.005). AUC pain scores on movement were 1197 (429) and 849 (395) mm h and on coughing were 1150 (378) and 884 (298) mm h in the placebo and meloxicam groups, respectively (both P<0.05). Nine patients in the placebo group and 12 in the meloxicam

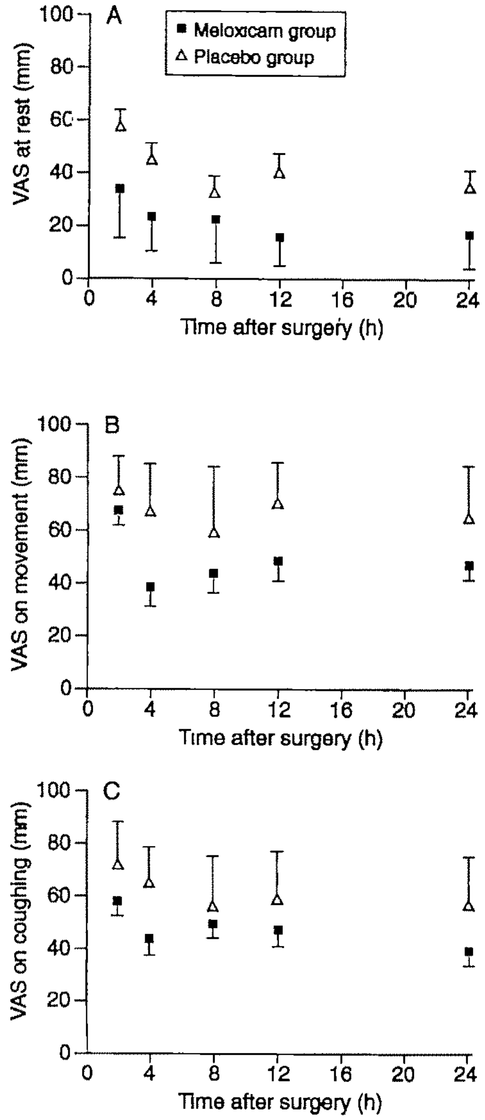


Fig 1 Mean (SD) visual analogue scores (VAS) for pain at rest (A), on movement (sitting from a lying position) (B) and on deep inspiration and coughing (C) during the first 24 h after surgery in the meloxicam and placebo groups. Comparison of AUC for 0–24 h showed significant differences between groups (P<0.005 pain at rest, P<0.05 pain on movement and on coughing)

group required antiemetic treatment, but no patient in either group vomited during the first 24 h after surgery.

Discussion

In patients undergoing abdominal hysterectomy, meloxicam 15 mg rectally before surgery produced a significant reduction in postoperative pain scores, although PCA morphine consumption in the first 24 h after surgery was not decreased significantly. There were no differences between groups in the incidence of adverse effects, which may reflect similar morphine requirements.

Most, but not all, studies comparing the postoperative analgesic effect of different non-selective NSAID have shown a decrease in opioid requirements, pain intensity, or both, despite using a variety of drugs, dose regimens and surgical procedures.[11] Morphine consumption was reduced by 50% in patients undergoing abdominal hysterectomy who had received rectal diclofenac 100 mg at the end of surgery and repeated at 12-h intervals for 3 days.[9] Hodsman and colleagues found that administration of diclofenac 75 mg i.m. immediately after major abdominal surgery and repeated 12 h later reduced PCA morphine consumption.[8] However, pain scores were similar to the placebo group 8–24 h after surgery. In our hospital, patients are encouraged to eat and drink 24 h after total abdominal hysterectomy and the PCA system is routinely discontinued at this time. Therefore, we chose to limit our study to the first 24 h after surgery, although differences in morphine consumption may have become apparent during a longer period of follow-up.

Power calculations for sample size were based on data from similar patients undergoing total abdominal hysterectomy recently in Leicester using a similar anaesthetic technique. Mean postoperative morphine requirements in this study were lower than observed previously, with large inter-individual variations. Consequently, the power of these data to demonstrate a difference in morphine requirements was lower than anticipated. Possible explanations for this difference include involvement of different surgeons, anaesthetists, ward and acute pain nursing staff, and administration of routine antiemetic prophylaxis to previous patients. PCA morphine consumption may have been limited by factors other than pain (e.g. nausea), although nausea scores and antiemetic requirements were also low. Previous studies investigating the effects of NSAID on perioperative analgesia have found different effects on analgesia and opioid consumption,[11] and larger studies may be required.

Meloxicam is highly (99.5%) bound to plasma proteins with a small volume of distribution (10–15 litre), low clearance (0.42–0.48 litre h^{-1}) and a long terminal elimination half-life ($T_{1/2}{}^{\beta}$=20–22 h) which allows once-daily dosing. Maximum plasma concentrations (*C*max=0.95 mg $litre^{-1}$ after 15 mg dose) are achieved approximately 5 h after oral or rectal administration and are higher (*C*max=1.72 mg $litre^{-1}$) after repeated or higher doses.[12] It is possible that alternative regimens (administration several hours before surgery, higher doses or repeated doses after operation) might have resulted in lower pain scores or morphine requirements, but in this pilot study we wished to establish the efficacy of the recommended dose (15 mg) in the perioperative setting.

The relative preference of meloxicam for COX-2 compared with COX-1 is estimated as 3–77:1, depending on the model used.[1] Relative COX-2:COX-1 selectivity ratios of 10–13:1 have been demonstrated in humans.[5 13] Other more specific inhibitors for COX-2 are becoming available (e.g. celecoxib and rofecoxib). Celecoxib has a relative COX-2:COX-1 selectivity ratio of approximately 375:1, and has recently been approved for use in osteoarthritis and rheumatoid arthritis. In patients undergoing tooth extraction under local anaesthesia, celecoxib was as effective as aspirin in providing postoperative analgesia.[1] Rofecoxib has a COX-2:COX-1 selectivity ratio >800:1. Recently published data have shown that it has similar efficacy to ibuprofen after dental extraction.[14] Both of these drugs may have advantages over meloxicam in terms of a further decrease in the incidence of adverse gastrointestinal and renal effects, but few data are available. There have been no published studies of their use in patients undergoing major surgery, and their efficacy, incidence of adverse effects and possible advantages over non-selective NSAID in the perioperative period are not yet established.

This pilot study is the first demonstration of the effectiveness of a COX-2 preferential NSAID in patients undergoing major surgery. Traditional non-selective NSAID are used widely in the perioperative period as they decrease opioid requirements and improve analgesia. If effective in this setting, the use of COX-2 preferential or COX-2 specific NSAID may provide advantages over traditional NSAID, particularly in the elderly and those at risk of the adverse gastrointestinal or renal effects of these drugs. Further studies are required to establish the efficacy and optimal dose regimens of COX-2 preferential or COX-2 specific NSAID in patients undergoing major surgery.

References

1 Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353**: 307–14

2 Vane JR. Mechanism of action of NSAIDs. *Br J Rheumatol* 1996; **35** (Suppl. 1): 1–3

3 Frolich JC. A classification of NSAIDs according to the relative inhibition of cyclooxygenase isoenzymes. *Trends Pharmacol Sci* 1997; **18**: 30–4

4 Engelhardt G. Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. *Br J Rheumatol* 1996; **35** (Suppl. 1): 4–12

5 Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam. *Clin Pharmacokinet* 1999; **36**: 115–26

6 Hawkey C, Kahan A, Steinbruck K, *et al.* Gastrointestinal tolerability of the COX-2 inhibitor, meloxicam in osteoarthritis patients: the meloxicam large scale international study safety assessment (MELISSA) *Br J Rheumatol* 1998; **37**: 937–45

7 Dequeker J, Hawkey C, Kahan A, *et al.* Improvement in gastrointestinal tolerability of the selective cyclooxygenase

(COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998, **37**: 946–51

8 Hodsman NB, Burns J, Blyth A, Kenny GN, McArdle CS, Rotman H. The morphine sparing effects of diclofenac sodium following abdominal surgery. *Anaesthesia* 1987; **42**: 1005–8

9 Scott RM, Jennings PN. Rectal diclofenac analgesia after abdominal hysterectomy. *Aust NZ J Obstet Gynaecol* 1997; **37**: 112–14

10 Guidelines on the use of NSAIDs in the perioperative period. London: Royal College of Anaesthetists, 1998

11 Dahl JB, Kehlet H. Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *Br J Anaesth* 1991; **66**: 703–12

12 Turck D, Roth W, Busch U. A review of the clinical pharmacokinetics of meloxicam. *Br J Rheumatol* 1996; **35** (Suppl. 1): 13–16

13 Noble S, Balfour JA. Meloxicam. *Drugs* 1996; **51**: 424–30

14 Ehrich EW, Dallob A, De Lepeleire I, *et al.* Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; **65**: 336–47

British Journal of Anaesthesia 84 (2): 155–62 (2000)

Differential effects of systemically administered ketamine and lidocaine on dynamic and static hyperalgesia induced by intradermal capsaicin in humans

H. Gottrup[1]*, P. O. Hansen[1], L. Arendt-Nielsen[2] and T. S. Jensen[1]

[1]*Department of Neurology, University Hospital of Aarhus, DK-8000 Aarhus, Denmark and Danish Pain Research Centre, University of Aarhus, DK-8000 Aarhus, Denmark.* [2]*Centre for Sensory–Motor Interaction, University of Aalborg, DK-9220 Aalborg, Denmark*

**Corresponding author: Danish Pain Research Centre, Bygning 1C, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark*

We have examined the effect of systemic administration of ketamine and lidocaine on brush-evoked (dynamic) pain and punctate-evoked (static) hyperalgesia induced by capsaicin. In a randomized, double-blind, placebo-controlled, crossover study, we studied 12 volunteers in three experiments. Capsaicin 100 μg was injected intradermally on the volar forearm followed by an i.v. infusion of ketamine (bolus 0.1 mg kg^{-1} over 10 min followed by infusion of 7 μg kg^{-1} min^{-1}), lidocaine 5 mg kg^{-1} or saline for 50 min. Infusion started 15 min after injection of capsaicin. The following were measured: spontaneous pain, pain evoked by punctate and brush stimuli (VAS), and areas of brush-evoked and punctate-evoked hyperalgesia. Ketamine reduced both the area of brush-evoked and punctate-evoked hyperalgesia significantly and it tended to reduce brush-evoked pain. Lidocaine reduced the area of punctate-evoked hyperalgesia significantly. It tended to reduce VAS scores of spontaneous pain but had no effect on evoked pain. The differential effects of ketamine and lidocaine on static and dynamic hyperalgesia suggest that the two types of hyperalgesia are mediated by separate mechanisms and have a distinct pharmacology.

Br J Anaesth 2000; **84**: 155–62

Keywords: pharmacology, capsaicin; anaesthetics local, lidocaine; anaesthetics i.v., ketamine; pain, experimental; pain, mechanism; complications, hyperalgesia

Accepted for publication: August 24, 1999

Hyperalgesia to mechanical stimuli is an essential part of many chronic pain conditions.[1–4] Experimentally, different types of mechanical hyperalgesia can be distinguished.[2 5–7] LaMotte and colleagues[5] described two types of mechanical hyperalgesia in a capsaicin model: a large hyperalgesic area to normally painful punctate stimuli and a smaller tender area which was painful to stroking stimuli. Kilo and colleagues[7] provided evidence for at least four types of mechanical hyperalgesia: one induced by gently brushing, one by punctate stimuli, one by blunt pressure and one by impact stimuli. While the two former types were suggested to depend on central sensitization resulting from central plastic changes, it was suggested that the latter two were caused by sensitization of peripheral nociceptors.

In neuropathic pain patients, different types of mechanical hyperalgesia can also be delineated. Ochoa and Yarnitsky[2] described a dynamic and a static type, where the former was induced by gently brushing the injured area, whereas the static type was induced by punctate stimuli in the painful area. Several lines of evidence indicate that these two types of hyperalgesia depend on different mechanisms. First, on the basis of compression blocks it has been shown that the dynamic type is mediated by large myelinated A-beta fibres and the punctate form by unmyelinated C-fibres.[2 6 8] Second, while both dynamic and static hyperalgesia involve central plastic changes induced by peripheral nociceptor activity, the dynamic form seems to depend on persistent input from nociceptors, and the static form can persist without such nociceptor activity, because anaesthetizing an area with hypersensitivity induced by capsaicin abolishes brush-evoked hyperalgesia but not punctate-evoked hyperalgesia.[5] Third, in a recent clinical study in patients with neuropathic pain, it was shown that brush-evoked pain and punctate-evoked hyperalgesia were not related, although both types are probably maintained by heat sensitive nociceptors.[9] Taken together, it is likely that different neural mechanisms are responsible for mechanical hyperalgesia. Further insight into the mechanisms of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

hyperalgesia may be obtained by examination of the pharmacology of dynamic and static mechanical hyperalgesia.

Intradermal capsaicin, the pungent ingredient of chilli peppers, is a well known human experimental pain model to induce neurogenic inflammation. Capsaicin activates C-fibres causing an intense burning pain sensation and development of primary and secondary hyperalgesia.[10 11] The mechanism of secondary hyperalgesia is believed to be caused by central sensitization of wide dynamic range (WDR) neurones and subsequent dynamic changes in the central processing of mechanoreceptive input in A-beta fibres.[8]

Ketamine is a non-competitive NMDA receptor blocker which reduces the activity of sensitized WDR neurones in the dorsal horn of the spinal cord[12 13] and may also act peripherally.[14–17] Ketamine has been shown to block experimentally induced pain and mechanical hyperalgesia in the capsaicin model[18 19] and the burn injury model.[20 21] In patients suffering from different types of neuropathic pain, ketamine has been reported to reduce both static[22 23] and dynamic hyperalgesia.[24 25]

In contrast, lidocaine is a sodium channel blocker which reduces hyperalgesia induced by nerve injury and nociceptor produced central sensitization, with both a peripheral and central action.[26–28] Lidocaine also reduces experimental hyperalgesia in humans[29] and clinical hyperalgesia after nerve injury.[29–31]

If dynamic and static hyperalgesia are mediated by different mechanisms, ketamine and lidocaine should modulate static and dynamic hyperalgesia differently. The intradermal capsaicin model was used to test this hypothesis.[5 6 11]

Subjects and methods

We studied 12 healthy male volunteers in a randomized, double-blind, placebo-controlled crossover study. Informed written consent was obtained from all participants and the study was approved by the Local Ethics Committee and the Danish National Board of Health. Before the first experiment, capsaicin 50 µg was injected into the left volar forearm to familiarize subjects with capsaicin pain and the tests performed during each experiment. One subject developed allodynia lasting only a few minutes at the screening session and was not included in the study.

Intradermal capsaicin

Capsaicin (8-methyl N-vanillyl 6-nonamide) (Sigma, USA) was dissolved in Tween 80 UPS by heating.[11] Saline was added under sterile conditions to obtain a concentration of 5 mg ml^{-1}. Capsaicin 20 µl (100 µg) was injected using a 0.5-ml syringe fitted with a 27-gauge needle. Six radiating lines from the injection site with ticks at 1-cm intervals were drawn on the skin before injection of capsaicin. The angle between each line was 60°. A point was marked 3 cm proximal to the injection site.

All injections were carried out on the right volar forearm. In the first experiment, injection was carried out 5 cm proximal from the wrist and in subsequent sessions the injection was moved 1 cm proximal from the preceding injection site to avoid injection at the same site.

Thermal thresholds

All sensory tests were carried out by the same investigator (H. G.) in a quiet room (temperature 20–22°C) with the subject comfortably lying in bed.

Thermal thresholds were measured using the Somedic Thermotest (Somedic AB, Sweden). A Peltier thermode with an area of 12.5 cm^2 was applied to the skin with a fixed application pressure at the site of injection. Baseline temperature was set at 30°C with a thermal rate of change of 1°C s^{-1} and an inter-stimulus interval randomized between 4 and 6 s. The cut-off limit for warmth was 52°C. Heat detection thresholds (HDT) and heat pain threshold (HPT) were determined at the injection site before injection of capsaicin to ensure that capsaicin was not injected into desensitized skin. Subjects indicated when perception changed to warm or hot pain by pressing a button. The thermode automatically returned to baseline temperature when the button was pressed. One minute after injection of capsaicin and at the end of each treatment, HPT at the injection site was determined. Thresholds were defined as the average of three measurements.

Assessment of pain and hyperalgesia

Pain assessment

Spontaneous pain and evoked pain intensity were measured using a visual analogue scale (VAS 0–100 mm; 0=no pain, 100=unbearable pain). To assess brush-evoked pain, a cotton gauze was swept back and forth three times at the 3-cm point at a speed of 1–2 cm s^{-1} and the intensity was scored on a VAS scale. Punctate-evoked pain was assessed by bending a fixed von Frey hair (744.9 mN) (Semmes-Weinstein monofilaments, Stoelting, IL, USA) at the 3-cm point twice, at a rate of 1 Hz, and was scored in a similar manner. All measurements were performed at specific times and in the following order: (1) spontaneous pain intensity, (2) brush-evoked pain intensity, (3) punctate-evoked pain intensity, (4) area of brush-evoked hyperalgesia and (5) area of punctate-evoked hyperalgesia.

Areas of secondary hyperalgesia

The area of brush-evoked hyperalgesia was assessed by stroking a hand-held cotton gauze from the skin with normal sensation towards the injection site at a rate of approximately 1 cm s^{-1} and in steps of 1 cm. This was performed along the six radiating lines drawn on the skin before injection of capsaicin. Subjects were asked to report when the sensation changed to a sensation of tenderness or pain, and the distance from the injection site to this point was measured. On basis of the marked distances along the lines where sensation changed, a hexagon was drawn and the area calculated.

The area of punctate-evoked hyperalgesia was assessed by bending a hand-held von Frey hair (744.9 mN) towards the injection site in steps of 1 cm at a rate of 1 cm s^{-1}. Subjects were asked to report when the sensation became increasingly painful. The area was measured as described above, by outlining the borders and calculated from a drawn hexagon.

Drug infusion

On each of 3 examination days, separated by at least 1 week, subjects received, in a double-blind randomized manner, an i.v. infusion of ketamine 50 mg ml^{-1} (Ketalar, Parke-Davis), lidocaine 20 mg ml^{-1} (Lidokain, SAD) or saline 9 mg ml^{-1} (NaCl, SAD) diluted in isotonic saline. I.v. infusion started 15 min after injection of capsaicin via an infusion pump (Ivac 598, Kivex A/S, Denmark); each treatment session consisted of infusion of NaCl 3×100 ml, with or without drug, over 10, 20 and 20 min. The total infusion time did not exceed 55 min. Ketamine was given as a bolus infusion of 0.1 mg kg^{-1} over 10 min followed by two infusions of 7 μg kg^{-1} min^{-1}, each lasting 20 min. Lidocaine was given as a continuous infusion of 1.67 mg kg^{-1} over 10 min, followed by one infusion of 3.33 mg kg^{-1} over 20 min and one infusion of NaCl 100 ml over 20 min. Saline was infused in a similar manner with NaCl 100 ml over 10 min followed by two infusions of NaCl 100 ml over 20 min. To ensure blinding, the investigator who carried out the measurements during the study (H. G.) was not involved in drug infusion or in collecting reports of side effects.

ECG, heart rate and arterial pressure were monitored until the end of each study session.

Side effects

To ensure blinding, subjects were asked about side effects at specific times by a co-investigator (P. O. H.) who administered the infusion and was responsible for the blinding procedure. The investigator responsible for sensory testing (H. G.) was not informed of side effect reports. Reported side effects were graded on a three-point scale as weak, moderate or severe.

Statistical analysis

The study was carried out in a crossover design. The number of subjects needed to document an effect was calculated as nine ($\alpha=0.05$; $\beta=0.80$).

Differences in HDT and HPT between treatment groups were analysed by one-way ANOVA. HPT values before and after injection of capsaicin were compared using a paired *t* test in each treatment group.

Effect variables were spontaneous pain, pain evoked by brush end punctate stimuli and areas of brush-evoked and punctate-evoked hyperalgesia. Measurements were performed at specific times after injection of capsaicin. In each treatment session, a baseline was defined for each subject which was the measurement 15 min after injection of capsaicin (start of infusion). Subsequent measures were converted to percentage of baseline. For each treatment and each subject, the effect variables were plotted against time as a percentage of baseline values. Curves for each treatment group are presented in Figures 1B–5B in which median values at each time of measurement are shown.

Area under the curve (AUC) for each subject was calculated for 15–45 min after injection of capsaicin, corresponding to the measurements performed during infusion ($t=15$, 30, 45 min). Differences in AUC between treatment groups were analysed by non-parametric repeated analysis of variance on ranks (Friedmans test). AUC are presented as box plots, medians are indicated by horizontal lines and boxes show the 25th to 75th percentiles; 90% confidence intervals are presented as whiskers. $P<0.05$ was considered statistically significant.

Results

The mean dose of ketamine administered was 28.4 (SD 4.2) mg and the mean dose of lidocaine was 374.6 (58.4) mg. The infusion was stopped temporarily for 2 min because of dizziness 26 min after onset in one individual receiving lidocaine and 16 min after onset in another individual receiving ketamine. These data are included in the results because the infusion was stopped for only a short period and because both investigator and subjects were uninformed.

Thermal thresholds in the primary hyperalgesic area

Table 1 shows the effect of capsaicin on thermal thresholds. There was no difference in heat detection threshold (HDT) or heat pain threshold (HPT) before injection of capsaicin in the three groups. There was a significant reduction in HPT 1 min after capsaicin and at the end of the study compared with before capsaicin in all three groups, but there were no differences between groups.

Pain relief

Median VAS scores for spontaneous pain at the beginning of infusion were 33 (25th and 75th percentiles 23, 53) in the placebo group, 46 (39; 58) in the ketamine group and

Table 1 Heat detection threshold (HDT) and heat pain threshold (HPT) values in the lidocaine, ketamine and placebo groups *$P < 0.05$ (paired *t* test) from corresponding HPT value before capsaicin (cap.) ($\text{HPT}_{\text{before}}$). Values are mean (SEM)

	Treatment		
Thermal threshold	**Lidocaine**	**Ketamine**	**Placebo**
$\text{HDT}_{\text{before}}$	32.55 (0.321)	32.6 (0.480)	32.44 (0.317)
$\text{HPT}_{\text{before}}$	44.39 (0.565)	44.76 (0.507)	43.97 (0.789)
$\text{HPT}_{\text{1 min after cap}}$	36.82 (0.962)*	37.5 (1.114)*	36.48 (0.917)*
$\text{HPT}_{\text{105 min after cap}}$	40.76 (0.672)*	41.74 (0.500)*	41.08 (0.672)*

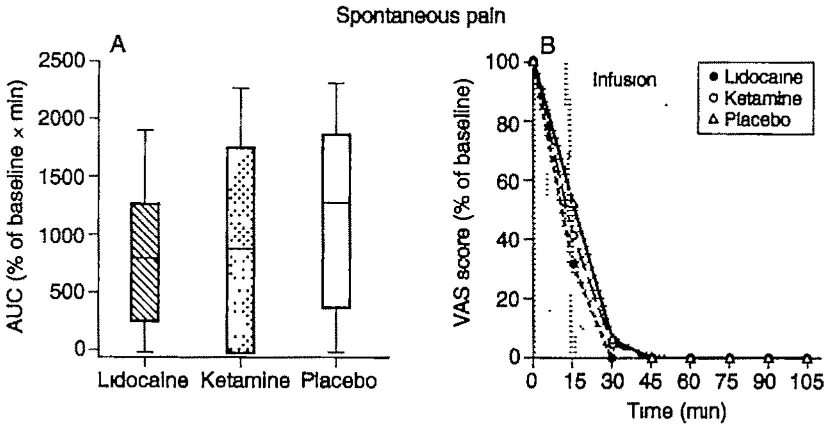


Fig 1 Spontaneous pain intensity in the lidocaine, ketamine and placebo groups, plotted as median AUC (A) and median VAS score (percentage of baseline) (B) from the start of infusion until the end of the experiment. The grey area indicates the infusion period (n=12).

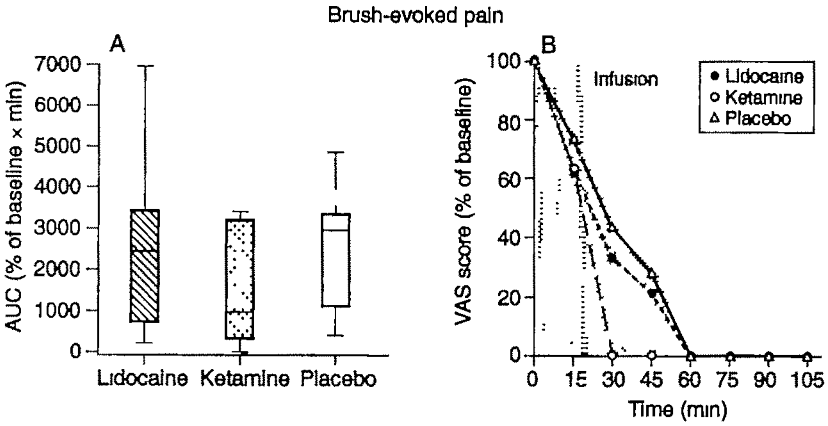


Fig 2 Intensity of brush-evoked pain in the lidocaine, ketamine and placebo groups, plotted as median AUC (A) and median VAS score (percentage of baseline) (B) from the start of infusion until the end of the experiment. The grey area indicates the infusion period (n=9).

41 (17; 55) in the lidocaine group. Lidocaine tended to reduce median VAS scores of spontaneous pain but this was not significant. There was no effect of ketamine or placebo on spontaneous pain. (Fig. 1A, B).

Brush-evoked pain

All subjects developed a short-lived brush-evoked pain outside the capsaicin injection site. Nine of 12 subjects still complained of pain in all three groups when brushing the skin at the 3-cm point immediately before drug infusion (15 min after capsaicin). The three subjects in whom brush-evoked pain disappeared before infusion started are not included in the results. VAS scores of brush-evoked pain at the beginning of the infusion were 25 (14; 40) in the placebo group, 26 (15; 43) in the ketamine group and 24 (10; 38) in the lidocaine group. There was no effect of lidocaine on brush-evoked pain whereas ketamine tended to reduce brush-evoked pain, although not significantly (Fig. 2A, B).

Punctate-evoked pain

All 12 subjects felt pain to a bending von Frey hair (744.9 mN) at a single point 3 cm proximal from the injection site. They were not asked to score the sensation before injection of capsaicin. VAS scores 15 min after capsaicin were 37 (21; 47) in the placebo group, 37 (25; 53) in the ketamine group and 29 (25; 50) in the lidocaine group. VAS scores for punctate-evoked pain at the 3-cm point were not reduced significantly by ketamine or lidocaine compared with placebo (Fig. 3A, B).

Area of hyperalgesia

Area of brush-evoked hyperalgesia

Eleven of 12 subjects still had an area of allodynia in all three experiments, 15 min after capsaicin. The subject without an area of allodynia 15 min after capsaicin was not included in the results. The median area of brush-evoked hyperalgesia at the beginning of the infusion was 26 (18;

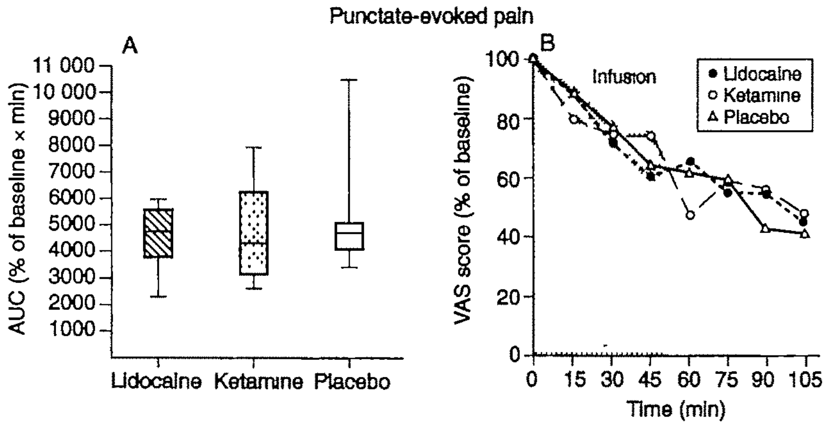


Fig 3 Intensity of punctate-evoked pain in the lidocaine, ketamine and placebo groups, plotted as median AUC (A) and median VAS score (percentage of baseline) (B) from the start of infusion until the end of the experiment. The grey area indicates the infusion period (n=12).

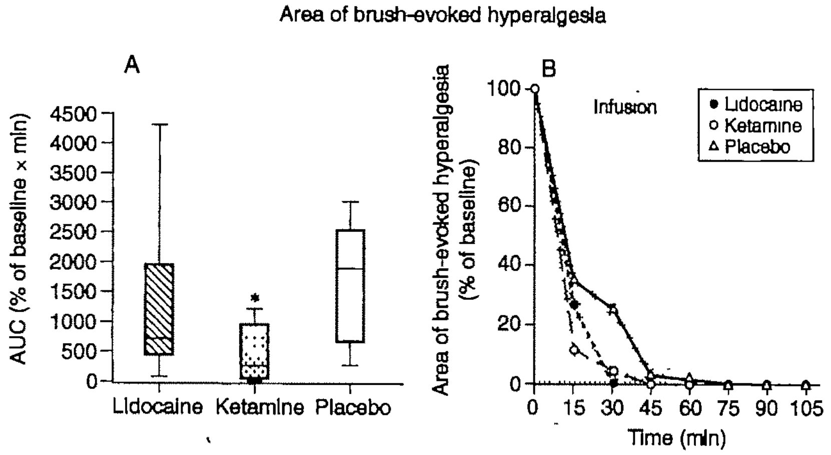


Fig 4 Area of brush-evoked hyperalgesia in the lidocaine, ketamine and placebo groups, plotted as median AUC (A) and median area (percentage of baseline) (B) from the start of infusion until the end of the experiment. The grey area indicates the infusion period (n=11). *Significant difference from corresponding placebo value (non-parametric repeated measures analysis of variance on ranks, Friedmans test, $P<0.05$).

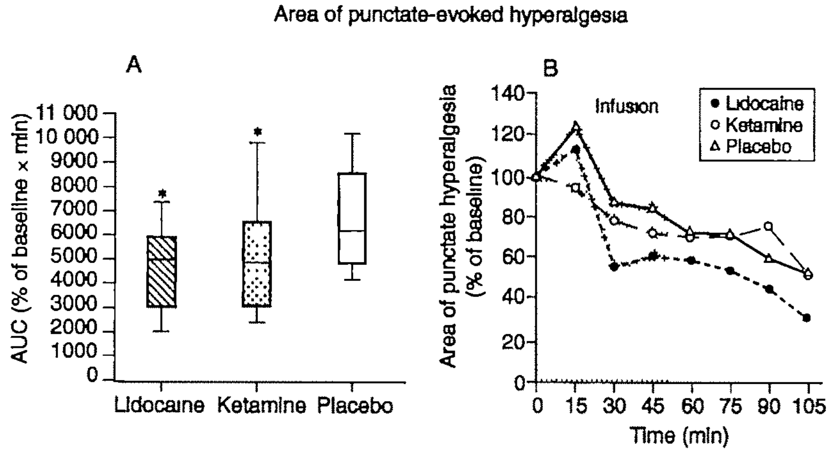


Fig 5 Area of punctate-evoked hyperalgesia in the lidocaine, ketamine and placebo groups, plotted as median AUC (A) and median area (percentage of baseline) (B) from the start of infusion until the end of the experiment. The grey area indicates the infusion period (n=12) *Significant difference from corresponding placebo value (non-parametric repeated measures analysis of variance on ranks, Friedmans test, $P<0$ 05)

33) cm^2 in the placebo group, 22 (19; 35) cm^2 in the ketamine group and 40 (23; 46) cm^2 in the lidocaine group. Ketamine, but not lidocaine, reduced the area of brush-evoked hyperalgesia significantly (non-parametric repeated measures analysis of variance on ranks, Friedmans test; $P<$ 0.05 ketamine *vs* placebo) (Fig. 4A, B).

Table 2 Number of subjects with side effects after drug treatment

	Ketamine	Lidocaine	Placebo
Paraesthesia	2	6	0
Dizziness	4	3	0
Sleepiness	1	2	0
Nausea	0	1	0
Dry mouth	0	3	0
Blurred vision	0	2	0
Light-headedness	0	2	0
Relaxed	5	1	0
Euphoria	1	0	0
Unreality	3	2	0
Drunkenness	3	4	0
Palpitations	0	2	0
'Flying'	2	0	0

Area of punctate-evoked hyperalgesia

All 12 subjects had an area of punctate-evoked hyperalgesia in each experiment. The area of punctate-evoked hyperalgesia at the beginning of the infusion was 22 (14; 45) cm^2 in the placebo group, 21 (15; 49) cm^2 in the ketamine group and 35 (29; 51) cm^2 in the lidocaine group. Both ketamine and lidocaine significantly reduced the area of punctate-evoked hyperalgesia during infusion (non-parametric repeated measures analysis of variance on ranks, Friedmans test, $P<0.05$ ketamine *vs* placebo; $P < 0.05$ lidocaine *vs* placebo) (Fig. 5A, B).

Side effects

During ketamine and lidocaine but not during saline treatment, subjects developed side effects. Table 2 shows the number of subjects reporting different types of side effects. Lidocaine caused paraesthesia and palpitations more frequently than ketamine, which produced more a feeling of relaxation, unreality, 'flying' and euphoria. In the ketamine group, one subject had three or more side effects, seven had two side effects and four had one side effect. In the lidocaine group, six subjects had three or more side effects, four had two side effects and two had one side effect. After infusion of ketamine, the intensity of the side effects were graded as weak in 19%, moderate in 67% and severe in 14% of subjects. After lidocaine infusion, side effects were graded as weak in 36%, moderate in 50% and severe in 19% of subjects.

Discussion

The main finding of our study was a differential effect of i.v. infusion of ketamine and lidocaine on brush-evoked hyperalgesia (dynamic hyperalgesia) and punctate-evoked hyperalgesia (static hyperalgesia).

We found that ketamine reduced the area of both brush-evoked and punctate-evoked hyperalgesia and tended to reduce the VAS score of brush-evoked pain but had no effect on spontaneous pain. Lidocaine reduced the area of punctate-evoked hyperalgesia but had no effect on the area of brush-evoked hyperalgesia or brush-evoked pain. Lidocaine tended to reduce spontaneous pain. Ketamine and lidocaine had no effect on VAS scores of punctate-evoked pain. Thus these findings extend, but are also at variance with, those obtained by others with lidocaine[32] and ketamine.[18]

Our findings suggested that: (1) central sensitization evoked by continuous noxious input from C-nociceptors was reduced by the NMDA antagonist ketamine; (2) a diminished noxious input, using a sodium channel blocker, reduced neuronal sensitization but did not prevent A-beta fibre input from driving already sensitized central neurones; and (3) the pharmacology of static and dynamic hyperalgesia can be distinguished.

Side effects were observed with both ketamine and lidocaine. Although it may be argued that blinding was insufficient, we consider this possibility unlikely. The examiner responsible for sensory testing and pain assessment was unaware of the reported side effects. The number of individuals with psychotropic side effects (sleepiness, light-headedness, relaxation, euphoria, unreality, 'flying' and drunkenness) was similar in the ketamine and lidocaine groups (Table 2). Finally, the differential effect of lidocaine and ketamine argues against systematic bias.

Experimental and clinical observations indicate that generation of pain in an injured area by mechanical input reflects central sensitization of WDR and spinothalamic tract neurones.[6–8 13 33 34] In our study, we measured two types of hyperalgesia: brush-evoked and punctate-evoked, which both reflect central sensitization, but which are probably mediated by separate mechanisms. Ochoa and Yarnitsky,[2] in a group of neuropathic patients, showed that the brush-evoked form was mediated by A-beta fibres while the punctate form was mediated by C-fibres. Punctate hyperalgesia outlasts capsaicin-induced pain and this hyperalgesia cannot be blocked by local lidocaine infiltration.[5] Finally, it has been shown recently in a series of neuropathic pain patients suffering from hyperalgesia that there was no relationship between brush-evoked pain and punctate-evoked pain in the same patients.[9]

The effect of ketamine is suggested to be a result of a central effect by non-competitive binding to NMDA receptors and hence block of sensitized WDR neurones in the spinal cord.[12 35 36] In our study, the areas of both brush-evoked hyperalgesia and punctate-evoked hyperalgesia were reduced by ketamine. Previous studies in experimental human pain models showed that NMDA block before and after injury reduced or abolished symptoms of central sensitization.[18 20–22] Our results are consistent with the findings of others in a burn injury model where the areas of both brush-evoked hyperalgesia and punctate hyperalgesia were reduced significantly after bolus infusion of ketamine.[18 20–22] Punctate, but not brush-evoked, hyperalgesia (allodynia) was reduced by post-injury treatment in the capsaicin model.[18] In our study, we failed to find a reduction in spontaneous or evoked pain, although ketamine tended to reduce brush-evoked pain. Differences in dose and timing of capsaicin and ketamine may be one explanation for this discrepancy. The fact that we used a very stiff von Frey hair when measuring evoked pain by punctate hyperalgesia may preclude us from finding an effect on punctate hyperalgesia.

Our study is consistent with clinical studies of ketamine showing relief of brush-evoked and punctate-evoked hyperalgesia in patients suffering from different types of neuropathic pain.[23–25]

Studies by Devor and colleagues indicated that lidocaine reduced ectopic discharges from distal neuromas and from ectopic foci in dorsal root ganglion cells (DRG).[37–39] A central action has also been suggested because systemic lidocaine blocks the nociceptive flexor reflex in humans[29] and the C-fibre-evoked reflex in rats.[40] In our study, lidocaine reduced the area of punctate hyperalgesia and tended to reduce spontaneous pain, but brush-evoked pain and the area of brush-evoked allodynia were not affected. Our findings differ from those reported by Wallace and colleagues[32] in which lidocaine 3 μg ml^{-1}, administered before capsaicin, reduced heat hyperalgesia and the area of flare after intradermal capsaicin, but had no significant effect on the area of hyperalgesia to stroking or punctate stimuli or spontaneous pain intensity. Again, differences in dose and timing of capsaicin and lidocaine may play a role in the differential effect. The tendency to reduce spontaneous pain is consistent with an action on neuronal discharges from C-nociceptors or their corresponding DRG cells.[37–39] We found only a tendency to reduction of spontaneous pain; one explanation may be a too low pain intensity when infusion started, or spontaneous pain may have disappeared before the maximum effect of lidocaine. We cannot exclude block of axon conduction by lidocaine, but we consider this possibility less likely. The dose used in this study was too low to produce plasma concentrations of 10–15 μl ml^{-1}, which are considered necessary to block axon conduction.[41] Lidocaine did not change heat pain threshold in the affected area. Hence our findings are consistent with reduced central sensitization caused by diminished noxious input from C-nociceptors or from their corresponding DRG cells.

Clinical observations support the pain relieving effect of lidocaine. Thus lidocaine or their analogues reduced pain in patients with post-herpetic neuralgia,[31] trigeminal neuralgia,[42] diabetic neuropathy[30 43] and cancer-related pain.[44]

The fact that ketamine and lidocaine altered static and dynamic hyperalgesia in a different way indicates that the underlying pharmacology of the two types of hyperalgesia are separate. From our study, it is not possible to determine exactly how this occurs. However, it may be hypothesized that reduced afferent input from C-nociceptors from the capsaicin injury site by lidocaine reduces central sensitization which is reflected in both dynamic and static hyperalgesia. Failure of lidocaine to block the A-beta mediated hyperalgesia may be a result of an effect on central sensitization, which is reduced but still of sufficient magnitude to be driven by A-beta input. A reduction in C-fibre input, under these conditions, may block punctate hyperalgesia. In contrast, it is conceivable that block of central sensitized WDR neurones by the NMDA receptor blocker ketamine reduces both dynamic and static hyperalgesia driven by A-beta and C-fibre input, respectively.

In summary, our findings indicate that an ongoing C-fibre input induced central sensitization which was blocked by a NMDA receptor antagonist. Reduction of afferent input using a sodium channel blocker may reduce central sensitization. A rational approach for treatment of some types of pain may therefore be a combination of a sodium channel blocker and an NMDA receptor antagonist because of the differential effects of ketamine and lidocaine. Additional combination studies are necessary to test this hypothesis.

Acknowledgements

This study was supported by grants from: Danish Pain Research Centre, Danish Cancer Society (No 78400), the Danish National Research Foundation and the Danish Medical Research Council (No 120828–1). We thank Dr Flemming W. Bach for helpful comments.

References

1 Lindblom U, Verrillo RT. Sensory functions in chronic neuralgia. *J Neurol Neurosurg Psychiatry* 1979; **42**: 422–35

2 Ochoa JL, Yarnitsky D. Mechanical hyperalgesia in neuropathic pain patients: dynamic and static subtypes. *Ann Neurol* 1993; **33**: 465–72

3 Bennett GJ. Neuropathic pain. In: Wall PD, Melzack R, eds. *Textbook of Pain*. Edinburgh: Churchill Livingstone, 1994; 201–24

4 Jensen TS. Mechanisms of neuropathic pain. In: Campbell JN, eds. *Pain 1996—an Updated Review*. Seattle: IASP Press, 1996; 77–86

5 LaMotte RH, Shain CN, Simone DA, Tsai EFP. Neurogenic hyperalgesia: psychophysical studies of underlying mechanisms. *J Neurophysiol* 1991; **66**: 190–211

6 Koltzenburg M, Lundberg LER, Torebjork HE. Dynamic and static components of mechanical hyperalgesia in human hairy skin *Pain* 1992; **51**: 207–19

7 Kilo S, Schmelz M, Koltzenburg M, Handwerker HO. Different patterns of hyperalgesia induced by experimental inflammation in human skin. *Brain* 1994; **117**: 385–96

8 Torebjork HE, Lundberg LER, LaMotte RH. Central changes in processing of mechanoreceptive input in capsaicin-induced secondary hyperalgesia in humans. *J Physiol* 1992; **448**: 765–80

9 Gottrup H, Nielsen J, Arendt-Nielsen L, Jensen TS. The relationship between sensory thresholds and mechanical hyperalgesia in nerve injury. *Pain* 1998; **75**: 321–9

10 Kenins P. Responses of single nerve fibers to capsaicin applied to the skin. *Neurosci Lett* 1982, **29**: 83–8

11 Simone DA, Baumann TK, LaMotte RH. Dose-dependent pain and mechanical hyperalgesia in humans after intradermal injection of capsaicin. *Pain* 1989; **38**: 99–107

12 Woolf CJ, Thompson SWN. The induction and maintenance of central sensitisation is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**: 293–9

13 Coderre TJ, Katz J, Vaccarino AL, MelzackR. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–85

14 Carlton SM, Hargett GL, Coggeshall RE Localization and activation of glutamate receptors in unmyelinated axons of rat glabrous skin. *Neurosci Lett* 1995; **197**: 25–8

15 Zhou S, Bonasera L, Carlton SM. Peripheral administration of NMDA, AMPA or KA results in pain behaviours in rats. *NeuroReport* 1996; **7**: 895–900

16 Warncke T, Jørum E, Stubhaug A. Local treatment with N-methyl-D-aspartate receptor antagonist ketamine inhibits development of secondary hyperalgesia in man by a peripheral action. *Neurosci Lett* 1997; **227**: 1–4

17 Lawand NB, Willis WD, Westlund KN. Excitatory amino acid receptor involvement in peripheral nociceptive transmission in rats. *Eur J Pharmacol* 1997; **324**: 169–77

18 Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. *Pain* 1995; **63**: 163–72

19 Andersen OK, Felsby S, Nikolejsen L, Bjerring P, Jensen TS, Arendt-Nielsen L. The effect of ketamine on stimulation of primary and secondary hyperalgesic areas induced by capsaicin—a double-blind, placebo-controlled, human experimental study. *Pain* 1996; **66**: 51–62

20 Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. *Br J Anaesth* 1996; **76**: 829–34

21 Warncke T, Stubhaug A, Jørum E. Ketamine, an NMDA receptor antagonist, suppresses spatial and temporal properties of burn-injured secondary hyperalgesia in man: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1997; **72**: 99–106

22 Eide PK, Jørum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain* 1994; **58**: 347–54

23 Nikolajsen L, Hansen CL, Nielsen J, Keller J, Arendt-Nielsen L, JensenTS. The effect of ketamine on phantom pain: a neuropathic disorder maintained by peripheral input. *Pain* 1996; **67**: 69–77

24 Felsby S, Nielsen J, Arendt-Nielsen L, Jensen TS. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. *Pain* 1995; **64**: 283–91

25 Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: A double-blind comparison to alfentanil and placebo. *Clin Neuropharmacol* 1995; **18**: 360–8

26 Abram SE, Yaksh TL. Systemic lidocaine blocks nerve injury-induced hyperalgesia and nociceptor-driven spinal sensitisation in the rat. *Anesthesiology* 1994; **80**: 383–91

27 Sotgui ML, Castagna A, Lacerenza M, Marchettini P. Pre-injury lidocaine treatment prevents thermal hyperalgesia and cutaneous thermal abnormalities in rat model of peripheral neuropathy. *Pain* 1995; **61**: 3–10

28 Chaplan SR, Bach FW, Shafer SL, Yaksh TL. Prolonged alleviation of tactile allodynia by intravenous lidocaine in neuropathic rats. *Anesthesiology* 1995; **83**: 775–85

29 Bach FW, Jensen TS, Kastrup J, Stigsby B, Dejgard A. The effect of intravenous lidocaine on nociceptive processing in diabetic neuropathy. *Pain* 1990, **40**: 29–34

30 Kastrup J, Petersen P, Dejgard A. Intravenous lidocaine infusion. A new treatment of chronic diabetic neuropathy. *Pain* 1987; **28**: 69–75

31 Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia *Neurology* 1991; **41**. 1024–8

32 Wallace MS, Laitin S, Licht D, Yaksh TL. Concentration–effect relation for intravenous lidocaine infusions in human volunteers. *Anesthesiology* 1997; **86**: 1262–72

33 Simone SA, Baumann TK, Collins JG, LaMotte RH. Sensitisation of cat dorsal horn neurons to innocuous mechanical stimulation after intradermal capsaicin. *Brain Res* 1989; **486**: 185–9

34 Simone DA, Sorkin LS, Oh U, Chung JM, LaMotte RH, Willis WD. Neurogenic hyperalgesia: Central neural correlates in responses of spinothalamic tract neurons. *J Neurophysiol* 1991; **66**: 228–45

35 Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following C fibre stimulation. *Neuropharmacology* 1987; **26**: 1235–8

36 Nagasaka H, Nagasaka I, Sato I, Matsumoto N, Matsumoto I, Hori T. The effect of ketamine on the excitation and inhibition of dorsal horn WDR neuronal activity induced by bradykinin injection into the femoral artery in cats after spinal cord transection. *Anesthesiology* 1993; **78**: 722–32

37 Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 1992; **48**: 261–8

38 Matzner O, Devor M. Hyperexcitability at sites of nerve injury depends on voltage-sensitive Na$^+$ channels. *J Neurophysiol* 1994; **72**: 349–59

39 Sotgui ML, Biella G, Castagna A, Lacerenza M, Marchettini P Different time-courses of iv lidocaine effect on ganglionic and spinal units in neuropathic rats. *NeuroReport* 1994; **5**: 873–6

40 Woolf CJ, Wiesenfeld-Hallin Z. The systemic administration of local anaesthetics produces a selective depression of C-afferent fibre evoked activity in the spinal cord. *Pain* 1985; **23**: 361–74

41 Darrell LT, MacIver MB. Analgesic concentrations of lidocaine suppress tonic A-delta and C fiber discharges produced by acute injury. *Anesthesiology* 1991; **74**: 934–6

42 Lindstrom P, Lindblom U. The analgesic effect of tocainide in trigeminal neuralgia. *Pain* 1987; **28**: 45–50

43 Dejgard A, Petersen P, Kastrup J. Mexiletine for treatment of chronic diabetic neuropathy. *Lancet* 1988; **1**· 9–11

44 Brose WG, Cousins MJ. Subcutaneous lidocaine for treatment of neuropathic cancer pain. *Pain* 1991; **45**: 145–8

British Journal of Anaesthesia **84** (2) 163–8 (2000)

Effect of alkalinization of lidocaine on median nerve block

D. G. Ririe[1], F. O. Walker[2], R. L. James[1] and J. Butterworth[1]*

[1]Department of Anesthesiology and [2]Department of Neurology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA

**Corresponding author*

Median nerve blocks were performed in 10 volunteers in a randomized, double-blind, crossover study to compare the effects of 1% plain lidocaine with 1% lidocaine in sodium bicarbonate 0.1 mmol litre^{-1}. Sensations of hot, cold, pinprick and light touch, compound motor and sensory nerve action potentials, and skin temperature were assessed at 2-min intervals. pH was 6.4±0.1 for plain lidocaine and 7.7±0.2 for alkalinized lidocaine ($P<0.001$). Alkalinized lidocaine produced more rapid inhibition of compound motor action potentials than plain lidocaine (median 4 (range 2–6) *vs* 9 (2–14) min) ($P=0.039$). Alkalinized lidocaine also produced more rapid onset of inhibition of compound motor than sensory nerve action potentials (4 (2–6) *vs* 8 (4–12) min) ($P=0.0039$). There was no significant difference in any other sensory modality between alkalinized and plain lidocaine. These data suggest that addition of bicarbonate to lidocaine for median nerve block significantly increased the rate of motor block without changing the onset or extent of sensory block.

Br J Anaesth 2000; **84**: 163–8

Keywords: anaesthetics local, lidocaine; nerve, block; formulations, lidocaine; formulations, pH

Accepted for publication: September 23, 1999

Different sensory modalities, such as sensations of touch, cold, warm and pain, have been known to be inhibited with different delays after application of local anaesthetics to nerves.[1] This phenomenon of different susceptibility of nerve modalities to local anaesthetics is known as differential nerve block. During regional anaesthesia, differential block can be observed during onset, at steady-state and during offset, and drug effects at all three times may guide local anaesthetic selection. For surgical anaesthesia, analgesia is paramount, but the extent of motor nerve block and speed of onset often determines the efficiency and success of the block. However, the labouring parturient seeks rapid onset of analgesia with minimal motor block. Patients suffering from myofascial pain disorders may benefit from selective block of motor nerves while maintaining sensory function. Therefore, understanding differential and steady-state block and interpreting findings of block of specific modalities with specific local anaesthetics are critical to achieving greater success with regional anaesthesia and analgesia.

Altering pH can modify the properties of local anaesthesia during onset of block or at steady state.[2–5] Numerous studies have reported increased potency and more rapid onset of block with alkalinized local anaesthetics.[6–13] However, the effect of alkalinization of local anaesthetics on differential nerve block has not been studied using multiple modality testing. In this study, we have assessed inhibition of median nerve fibre transmission using both objective sensory, motor and multiple modality subjective sensory data as we have done in previous studies.[14–16] Here, we measured onset of block of the median nerve with lidocaine to test our hypothesis that addition of bicarbonate uniformly speeds the onset of anaesthesia in all modalities. Our data rejected this hypothesis as we observed a significant reduction in the delay of onset of motor block, without a commensurate change in the onset of sensory block.

Subjects and methods

After obtaining approval from the Clinical Research Practices Committee and informed consent, we studied 10 volunteers undergoing bilateral median nerve block. No subject had clinical or electrodiagnostic findings consistent with median nerve dysfunction. Both dominant and non-dominant median nerves were studied in random order.

Median nerve block was performed after preparation of the skin with isopropyl alcohol. A 22-gauge B-bevel needle was used. The needle was inserted lateral to the palmaris longus tendon on the volar aspect of the wrist and advanced until it was felt to pass through the flexor retinaculum. Paraesthesia was not sought, and if it occurred, the needle was repositioned. Plain lidocaine HCl 1% (5 ml) (Astra Pharmaceuticals, Westboro, MA, USA) mixed with normal saline 0.1 ml ml^{-1} or sodium bicarbonate 100 mmol litre^{-1} (8.4% $NaHCO_3$ 0.1 ml ml^{-1}) was injected over 30–45 s

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

after negative aspiration. Both subjects and investigators were blinded to the solution injected. Measurement of pH was performed in all solutions using a standard pH probe.

Using a Nicolet Viking (Madison, WI, USA), the median nerve was serially stimulated at the wrist, 2 cm proximal to the site of local anaesthetic injection. Compound muscle action potentials (CMAP) were recorded using belly tendon electrodes over the abductor pollicis brevis and sensory nerve action potentials (SNAP) were recorded using ring electrodes at the base and distal end of the third digit (middle finger).[14 15 17] All stimuli were supramaximal, as determined by ramping stimulus intensity to 20% above that required to detect any further change in response amplitude. The response amplitudes of SNAP and CMAP represent the function of $A\alpha$ sensory and motor fibres, respectively. Unmyelinated C fibre function was assessed using measurements of skin temperature at the distal end of the index finger with a thermistor accurate to 0.1°C. Light touch sensibility was assessed using Von Frey hairs.[18] Sensation to pinprick, hot and cold was assessed on the proximal aspect of the palmar surface of the third digit compared with the same stimulus delivered on the volar aspect of the forearm, halfway between the wrist and the elbow, and recorded as a percentage of baseline sensation in the forearm.

Baseline measurements of all modalities were recorded. After injection of the local anaesthetic, all modalities were assessed at 2-min intervals until no change was observed over 10 min or until 30 min had elapsed. As end-points to assess differences in block, we used (1) time to the first noticeable difference, (2) time to half normal effects and (3) area under the effect *vs* time curve.

We chose to study 10 volunteers, assuming that the variability in measurements would be comparable with that in previous studies, and that the difference which we wished to detect was (at a minimum) comparable with that between saline and 0.25% lidocaine. A power analysis was performed based on a one-sided Fisher's sign test (we assumed that alkalinization would not increase the delay of onset). Assuming that the latency of one drug would be greater than the other drug 90% of the time, we calculated that a sample size of eight patients should find a significant difference with 81% power.

The pH of the local anaesthetic is reported as mean (SEM). A t test was used to determine pH differences. All other values are expressed as median (range). Statistical significance was tested for all objective and subjective motor and sensory modalities using Fisher's sign test. Confidence intervals for drug differences with respect to each end-point were determined using Thompson's method.[19] Statistical analysis was performed using the SAS (SAS Institute, Cary, NC, USA) program. $P<0.05$ was judged significant.

Results

pH was 6.4 (0.1) ($n=10$) for plain lidocaine and 7.7 (0.2) ($n=10$) for alkalinized lidocaine ($P<0.001$).

Table 1 Time delay (min) until first noticeable difference after injection of lidocaine or lidocaine+bicarbonate *Confidence=degree of confidence, CI= confidence interval Lidocaine+bicarb=Lidocaine plus bicarbonate; CMAP= compound motor action potentials, SNAP=sensory nerve action potentials, Difference=differences between onset time with lidocaine and with lidocaine+bicarb †One-sided Fisher's sign test

	Median (range)	**Confidence (CI) (%)***	***P*†**
Cold			
Lidocaine	4 (0, 20)		
Lidocaine+bicarb	4 (2, 20)		
Difference	0 (–16, 6)	98 (–16, 2)	0.50
Hot			
Lidocaine	2 (2, 20)		
Lidocaine+bicarb	3 (2, 8)		
Difference	0 (–16, 4)	94 (–16, 2)	0.50
Pinprick			
Lidocaine	3 (2, 8)		
Lidocaine+bicarb	4 (2, 20)		
Difference	1 (–4, 12)	98 (–4, 4)	0.23
Temperature			
Lidocaine	3 (2, 10)		
Lidocaine+bicarb	8 (2, 18)		
Difference	2 (–2, 16)	97 (–2, 14)	0.11
Von Frey hairs			
Lidocaine	3 (2, 24)		
Lidocaine+bicarb	5 (2, 12)		
Difference	1 (–22, 8)	99 (–22, 4)	0.36
SNAP			
Lidocaine	2 (2, 4)		
Lidocaine+bicarb	2 (2, 4)		
Difference	0 (–2, 2)	97 (–14, 2)	0.50
CMAP			
Lidocaine	2 (2, 6)		
Lidocaine+bicarb	2 (2, 4)		
Difference	0 (–4, 2)	94 (–4, –2)	0.19

There were no differences between alkalinized and plain lidocaine in the time delay until a 'just noticeable' difference was detected after injection (Table 1). Increasing the pH of the lidocaine solution had a significant effect only on CMAP inhibition (Table 1). Alkalinization had no effect on median time to the first noticeable difference for CMAP, which was 2 (range 2–6) min for plain lidocaine compared with 2 (2–4) min for alkalinized lidocaine. Similarly, alkalinization had no effect on median time to first noticeable difference in SNAP (2 (2–4) min for plain *vs* 2 (2–4) min for alkalinized lidocaine). Furthermore, there was no significant difference between motor block (as measured by CMAP) and sensory block (as measured by SNAP) with either plain or alkalinized lidocaine for the time to first noticeable difference.

Inhibition of CMAP occurred more rapidly with alkalinized than plain lidocaine (Table 2). Time to half maximal effect was significantly reduced with alkalinized (4 (2–6) min) compared with plain (9 (2–14) min) lidocaine ($P=0.02$). Motor and sensory block were achieved at approximately the same rate with plain lidocaine; thus there was no difference between CMAP and SNAP for time to

Table 2 Time delay (min) until half of the maximal effect was observed after injection of lidocaine or lidocaine+bicarbonate. *Confidence=Degree of confidence, CI=confidence interval. Lidocaine+bicarb=Lidocaine plus bicarbonate; CMAP=compound motor action potentials; SNAP=sensory nerve action potentials; Difference=differences between onset times with lidocaine and with lidocaine+bicarb †One-sided Fisher's sign test; ‡onset of SNAP and CMAP significantly different ($P<0.02$)

	Median (range)	Confidence (CI) (%)*	P†
Cold			
Lidocaine	10 (0, 20)		
Lidocaine+bicarb	7 (4, 20)		
Difference	1 (–16, 8)	96 (–8, 6)	0.36
Hot			
Lidocaine	5 (2, 20)		
Lidocaine+bicarb	6 (2, 12)		
Difference	0 (–16, 8)	97 (–16, 8)	0.38
Pinprick			
Lidocaine	8 (2, 20)		
Lidocaine+bicarb	8 (2, 20)		
Difference	1 (–16, 12)	96 (–4, 6)	0.30
Temperature			
Lidocaine	8 (2, 20)		
Lidocaine+bicarb	10 (2, 22)		
Difference	0 (–2, 20)	97 (–2, 6)	0.06
Von Frey hairs			
Lidocaine	8 (2, 24)		
Lidocaine+bicarb	10 (2, 20)		
Difference	0 (–16, 18)	98 (–16, 8)	0.45
SNAP			
Lidocaine	11 (4, 12)		
Lidocaine+bicarb‡	8 (4, 12)		
Difference	–1 (–8, 2)	97 (–8, –2)	0.08
CMAP			
Lidocaine	9 (2, 14)		
Lidocaine+bicarb‡	4 (2, 6)		
Difference	–4 (–10, 2)	96 (–8, –2)	0.008

Table 3 Area under the effects *vs* time curve after injection of lidocaine or lidocaine+bicarbonate *Confidence=Degree of confidence, CI=confidence interval Lidocaine+bicarb=Lidocaine plus bicarbonate, CMAP=compound motor action potentials, SNAP=sensory nerve action potentials, Difference=difference between onset times with lidocaine and with lidocaine+bicarb †One-sided Fisher's sign test; ‡onset of SNAP and CMAP significantly different ($P<0.02$)

	Median (range)	Confidence (CI) (%)*	P†
Cold			
Lidocaine	1663 (455, 3300)		
Lidocaine+bicarb	1145 (374, 2000)		
Difference	–244 (–1560, 115)	98 (–1300, –86)	0.05
Hot			
Lidocaine	1233 (321, 2800)		
Lidocaine+bicarb	1188 (260, 2800)		
Difference	–27 (–1000, 1200)	96 (–785, 184)	0.50
Pinprick			
Lidocaine	1195 (665, 2000)		
Lidocaine+bicarb	1381 (357, 2480)		
Difference	–10 (–718, 1220)	93 (–368, 196)	0.36
Temperature			
Lidocaine	2128 (1938, 2252)		
Lidocaine+bicarb	2019 (1930, 2262)		
Difference	–41 (–323, 128)	96 (–172, 49)	0.50
Von Frey hairs			
Lidocaine	2149 (1890, 3465)		
Lidocaine+bicarb	2175 (1795, 3013)		
Difference	–81 (–1343, 1013)	98 (–313, 317)	0.50
SNAP			
Lidocaine	1322 (523, 1654)		
Lidocaine+bicarb‡	1049 (409, 1453)		
Difference	–211 (–1013, 250)	98 (–526, 96)	0.17
CMAP			
Lidocaine	816 (308, 1682)		
Lidocaine+bicarb‡	387 (245, 1273)		
Difference	–492 (–1438, 842)	98 (–811, –414)	0.01

half maximal effect. Conversely, motor block was achieved more rapidly than sensory block with alkalinized lidocaine; time to half maximum effect for CMAP was 4 (2–6) min compared with 8 (4–12) min for SNAP ($P=0.0039$). These results were mirrored in our comparisons of area under the effect *vs* time curves (Table 3). After injection of alkalinized lidocaine, inhibition of CMAP (median area 387 (245–1273)) occurred significantly faster than that of SNAP (area 816 (308–1682)). The difference between plain and alkalinized lidocaine was also significant for CMAP. Nevertheless, at steady state, there was no difference in the degree of inhibition of SNAP and CMAP with either plain or alkalinized lidocaine (Fig. 1).

There were no differences between plain and alkalinized lidocaine for time of onset, time to half maximal effect or extent of steady-state inhibition of hot, cold or pinprick sensations (Fig. 2, Tables 1–3). Also, light touch perception, as measured using Von Frey filaments, showed similar onset and extent of inhibition (Tables 1–3). Skin temperature increased significantly after local anaesthesia, but in a similar manner in the two groups (Fig. 3, Tables 1–3).

Discussion

In this study, we used a previously established model to systematically test if alkalinization of lidocaine differentially altered multiple sensory nerve modalities or motor nerve function.[14–16] Quantitative and semi-quantitative objective and subjective data were collected. The median nerve was used as a simple and reproducible model of nerve block. Although multiple sensory modalities were tested, alkalinization had no significant effect. In contrast, alkalinization increased the speed of onset of motor nerve block, as measured objectively using CMAP.

Previous investigators have reported effects of alkalinized local anaesthetics on various types of nerve block.[6–13 20–24] Generally, these studies measured only the delay in onset of pinprick analgesia. Alkalinization has been shown to increase onset, potency and duration of block.[6–13] However, reports of no effect of alkalinization have also been published.[20–23] The effects of bicarbonate varied depending on the local anaesthetic used, other additives (e.g. epinephrine), type of nerve block, and the definitions used for onset and extent of nerve block. In some studies, a bicarbonate effect

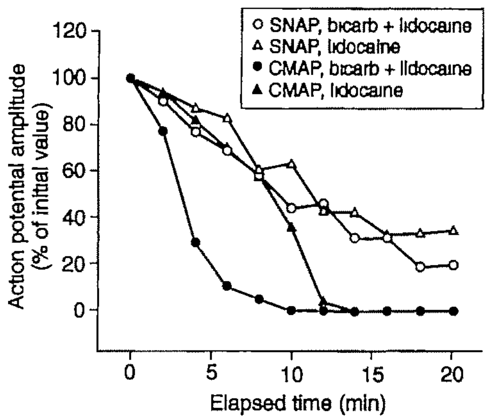


Fig 1 Effects of plain lidocaine and lidocaine with bicarbonate (bicarb) on sensory nerve action potentials (SNAP) and compound motor action potentials (CMAP) Data are percentage of the initial amplitude of the action potential waveform elicited by supramaximal simulation of the median nerve. Lidocaine with bicarbonate produced a significant effect on CMAP (P=0.02), as measured by time to half maximum effect The effect of bicarbonate on CMAP was different than that on SNAP (P<0.02). There was no effect of bicarbonate inhibition of SNAP and there was no significant difference between SNAP and CMAP after injection of plain lidocaine. At steady state, inhibition was similar for plain lidocaine and lidocaine with bicarbonate. All data are median values.

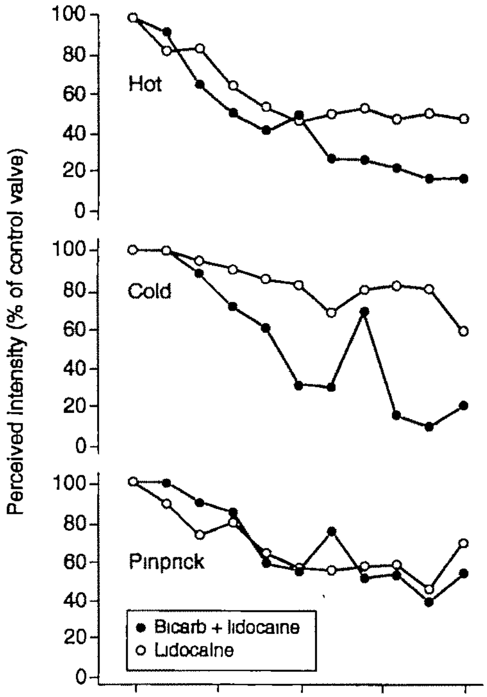


Fig 2 Effects of plain lidocaine and lidocaine with bicarbonate (bicarb) on perception of pinprick, hot and cold. Subjects described the intensity of stimulation in anaesthetized skin as a percentage of perceived intensity in a constant region of unanaesthetized skin. Initially, perceived intensity was the same at the two sites, which was recorded as 100% No difference was found between plain lidocaine or lidocaine with bicarbonate for hot, pinprick and cold sensibility. All data are median values.

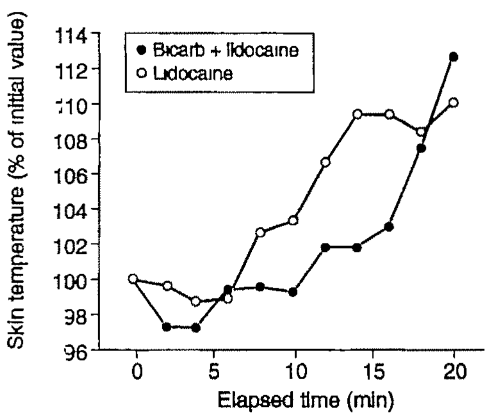


Fig 3 Effects of plain lidocaine and lidocaine with bicarbonate (bicarb) on skin temperature Data are percentage of the initial temperature (°C). There was no difference between plain lidocaine and lidocaine with bicarbonate. Consistent with our previous experience, most subjects demonstrated a decline in skin temperature, presumably from a sympathetic response to the pain of injection, before demonstrating an increase in temperature as a result of C-fibre (or preganglionic B-fibre) inhibition and vasodilatation. Data are median values.

on speed of onset but not affecting the overall extent of block may have been overlooked.[21] Similarly, inability to detect differences between alkalinized and plain local anaesthetic may be a result of insensitive, qualitative measures of motor and sensory block.[20] Finally, the conflicting results may be attributable partially to the differential effect of the alkalinization on sensory and motor nerve fibres. Repeated testing over time, attention to speed and overall or steady-state block, use of objective data and multiple modality subjective testing puts our results in context with other study designs. In light of our observations, most likely only onset of motor block was significantly hastened by alkalinization with bicarbonate for median nerve block (and probably other peripheral nerve blocks also). Furthermore, the difference detected was transient, occurring only during onset and only with a single modality.

In our study, addition of sodium bicarbonate to lidocaine significantly increased the solution pH, which may affect local anaesthetic block in several ways. Increasing extracellular pH with a constant extracellular local anaesthetic concentration results in greater intracellular local anaesthetic concentration and more complete inhibition of sodium currents, whether or not intracellular carbon dioxide or pH changes.[25] When extracellular pH is increased by addition of bicarbonate, decreased intracellular pH through diffusion of carbon dioxide (produced from the reaction of H^+ and HCO_3^- in extracellular fluid) may also play a role in enhancing local anaesthetic block through protonation of intracellular free-base local anaesthetic ('ion trapping') and increasing the concentration gradient for the free-base local anaesthetic across the plasma membrane.[4] In addition, bicarbonate ions probably non-specifically reduce the margin of safety for nerve conduction and may have a direct action on local anaesthetic binding to the sodium channel.[26]

However, the role of these various effects in producing differential motor *vs* sensory nerve block is unclear, particularly during regional anaesthesia in humans.

Why should bicarbonate influence the onset of motor but not sensory nerve block? It is possible that responses to bicarbonate may differ depending on the local anaesthetic. Etidocaine, an anaesthetic with many structural similarities to lidocaine, seems to preferentially inhibit motor fibres during onset and offset of regional block.[27] It is possible that bicarbonate merely accentuates a subtle motor:sensory difference inherent to this 'family' of related compounds. In contrast, there may be structural differences between sodium channels in motor and sensory fibres. Perhaps, sodium channels in motor fibres are more heavily glycosylated than those in sensory fibres, partially 'shielding' the sodium channel from local anaesthetic. The more membrane-permanent free-base form, favoured over the protonated form by bicarbonate, should have a more rapid onset under such circumstances. Sodium channel isoforms differ between nerve and muscle fibres; they may also differ between motor and sensory nerve fibres.[28, 29]

Local anaesthetic solutions pre-packaged with epinephrine appear to show greater effect from alkalinization than plain local anaesthetic solutions.[9, 23] As a result, in some studies, alkalinization of local anaesthetic in the absence of epinephrine has had no significant effect on block whereas significant differences were noted with epinephrine–local anaesthetic mixtures.[9, 23, 30] In our study, plain lidocaine was compared with epinephrine-free alkalinized lidocaine, and significant differences were found only for motor block. We recognize that different results may have been obtained had we conducted our study using lidocaine solutions pre-packaged with epinephrine.

Our results suggest that median nerve motor fibres are more sensitive to the effects of alkalinization of lidocaine than sensory fibres. We observed more rapid onset of motor nerve block, measured objectively using CMAP, after alkalinization of lidocaine, with no significant effect on SNAP or any other sensory modality. These results contrast with epidural studies where both modalities were potentiated equally.[11–12] We found an effect of bicarbonate only during onset of block but not at steady state. Our inability to show differences at steady state most likely relates to the relatively concentrated solutions of lidocaine used. We anticipated that 1% plain lidocaine would produce nearly complete block of SNAP and CMAP, thus making it difficult to demonstrate increased block at steady state when bicarbonate was added to the local anaesthetic. Thus we cannot exclude the possibility that addition of bicarbonate may increase the potency of lower concentrations of lidocaine at steady state.

Our results suggest that alkalinization of plain lidocaine for median nerve block provides no benefit beyond more rapid and, possibly, more profound motor block. In addition, when alkalinized lidocaine solution is used for block, motor block may be a reliable and early marker for the sensory block that is ultimately achieved.

References

1 Sinclair DC, Hinshaw JR. Sensory changes in procaine nerve block. *Brain* 1950; **73**: 224–43

2 Catchlove RF. Potentiation of two different local anaesthetics by carbon dioxide. *Br J Anaesth* 1973, **45**: 471–4

3 Bokesch PM, Raymond SA, Strichartz GR. Dependence of lidocaine potency on pH and PCO_2. *Anesth Analg* 1987, **66**. 9–17

4 Katsuki H, Ibusuki S, Takasaki M, Nagata K, Hiji Y. Monocarboxylic acids enhance the anesthetic action of procaine by decreasing intracellular pH. *Biochim Biophys Acta* 1997, **1334**: 273–82

5 Ritchie JM, Ritchi BR. Local anesthetics: effect of pH on activity. *Science* 1968, **162**: 1394–5

6 Tetzlaff JE, Yoon HJ, Brems J, Javorsky T. Alkalinization of mepivacaine improves the quality of motor block associated with interscalene brachial plexus anesthesia for shoulder surgery. *Reg Anesth* 1995; **20**: 128–32

7 Tetzlaff JE, Yoon HJ, O'Hara J, Reaney J, Stein D, Grimes-Rice M. Alkalinization of mepivacaine accelerates onset of interscalene block for shoulder surgery. *Reg Anesth* 1990; **15**: 242–4

8 Quinlan JJ, Oleksey K, Murphy FL. Alkalinization of mepivacaine for axillary block. *Anesth Analg* 1992; **74**: 371–4

9 Hilgier M. Alkalinization of bupivacaine for brachial plexus block. *Reg Anesth* 1985, **10**: 59–61

10 Gormley WP, Hill DA, Murray JM, Fee JP. The effect of alkalinisation of lignocaine on axillary brachial plexus anaesthesia. *Anaesthesia* 1996; **51**: 185–8

11 Benzon HT, Toleikis JR, Dixit P, Goodman I, Hill JA. Onset, intensity of blockade and somatosensory evoked potential changes of the lumbosacral dermatomes after epidural anesthesia with alkalinized lidocaine. *Anesth Analg* 1993; **76** 328–32

12 DiFazio CA, Carron H, Grosslight KR, Moscicki JC, Bolding WR, Johns RA Comparison of pH-adjusted lidocaine solutions for epidural anesthesia. *Anesth Analg* 1986, **65**: 760–4

13 Capogna G, Celleno D, Costantino P, Muratori F, Sebastiani M, Baldassini M. Alkalinization improves quality of lidocaine–fentanyl epidural anaesthesia for caesarean section. *Can J Anaesth* 1993; **40**: 425–30

14 Butterworth JF IV, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. *Anesthesiology* 1990; **72**. 962–5

15 Butterworth JF IV, Walker FO, Neal JM. Cooling potentiates lidocaine inhibition of median nerve sensory fibers. *Anesth Analg* 1990; **70**: 507–11

16 Butterworth J, Rine DG, Thompson RB, Walker FO, Jackson D, James RL. Differential onset of median nerve block. a randomised, double-blind comparison of mepivacaine with bupivacaine in healthy volunteers. *Br J Anaesth* 1998; **81**: 515–21

17 Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle. Principles and Practice*. Philadelphia: FA Davis, 1983

18 Head H. *Methods of Examining Sensation Studies in Neurology, vol I*. London: H Frowde, 1920; 12–17

19 Hollander M, Wolfe DA. A distribution-free confidence interval based on the sign test (Thompson, Savur). In. Hollander M, Wolfe DA, eds. *Nonparametric Statistical Methods* New York: John Wiley, 1973; 48–50

20 Chow MYH, Sia ATH, Koay CK, Chan YW. Aklalinization of lidocaine does not hasten the onset of axillary brachial plexus block. *Anesth Analg* 1998; **86**: 566–8

21 Darian-Smith I, Johnson KO, Dykes R. 'Cold' fiber population

innervating palmar and digital skin of the monkey: responses to cooling pulses. *J Neurophysiol* 1973; **36**: 325–46

22 Gaggero G, Meyer O, Van Gessel E, Rifat K. Alkalinization of lidocaine 2% does not influence the quality of epidural anaesthesia for elective caesarean section. *Can J Anaesth* 1995; **42**: 1080–4

23 Candido KD, Winnie AP, Covino BG, Raza SM, Vasireddy AR, Masters RW. Addition of bicarbonate to plain bupivacaine does not significantly alter the onset or duration of plexus anesthesia. *Reg Anesth* 1995; **20**: 133–8

24 Capogna G, Celleno D, Laudano D, Giunta F. Alkalinization of local anesthetics. Which block, which local anesthetic? *Reg Anesth* 1995; **20**: 369–77

25 Ibusuki S, Katsuki H, Takasaki M. The effects of extracellular pH with and without bicarbonate on intracellular procaine concentrations and anesthetic effects in crayfish giant axons. *Anesthesiology* 1998; **88**: 1549–57

26 Wong K, Strichartz GR, Raymond SA. On the mechanisms of potentiation of local anesthetics by bicarbonate buffer: drug structure–activity studies on isolated peripheral nerve. *Anesth Analg* 1993; **76**: 131–43

27 Covino BG, Vassallo HG. *Local Anesthetics: Mechanisms of Action and Clinical Use*. New York: Grune and Stratton, 1976

28 Wright SN, Wang SY, Kallen RG, Wang GK. Differences in steady-state inactivation between Na channel isoforms affects local anesthetic binding affinity. *Biophys J* 1997; **73**: 779–88

29 Nuss HB, Tomaselli GF, Marban E. Cardiac sodium channels (hH1) are intrinsically more sensitive to block by lidocaine than are skeletal muscle (µ1) channels. *J Gen Physiol* 1995; **106**: 1193–209

30 Bedder MD, Kozody R, Craig DB. Comparison of bupivacaine and alkalinized bupivacaine in brachial plexus anesthesia *Anesth Analg* 1988; **67**: 48–52

British Journal of Anaesthesia 84 (2). 169–73 (2000)

Postoperative pain management and recovery after remifentanil-based anaesthesia with isoflurane or propofol for major abdominal surgery

E. Kochs[1]*, D. Côté [2], L. Deruyck[3], V. Rauhala[4], M. Puig[5], E. Polati[6], J. Verbist[7], B. Upadhyaya[8], C. Haigh[8] and the Remifentanil Study Group

[1]*Technische Universität München, München, Germany.* [2]*Hôpital Laval, Ste-Foy, Québec, Canada.* [3]*AZ Sint Lucas, Ghent, Belgium.* [4]*Keski-Suomen Keskussairaala, Jyvaskyla, Finland.* [5]*Hospital del Mar, Barcelona, Spain.* [6]*Universita' degli Studi di Verona, Verona, Italy.* [7]*Glaxo Wellcome Belgium SA, Brussels, Belgium.* [8]*Glaxo Wellcome R&D, London, UK*

**Corresponding author: Klinik für Anaesthesiologie, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, D-81675 München, Germany*

We have assessed if recovery times after morphine or fentanyl, given before terminating remifentanil anaesthesia with isoflurane or propofol, are compromised We studied patients undergoing elective, major abdominal surgery, allocated randomly to receive remifentanil and isoflurane ($n=277$) or remifentanil and propofol ($n=274$) anaesthesia. Twenty-five minutes before the end of surgery, patients received fentanyl 0.15 mg or morphine 15 mg in a randomized, double-blind manner followed by a second dose (fentanyl 0.05 mg, morphine 7 mg) for moderate or severe pain in recovery. Recovery was rapid and at an Aldrete score ≥9 (median 12–15 min), 42–51% of patients reported none or mild pain. However, 26–35% of patients reported severe pain and >90% required a second dose of opioid within 21–27 min after anaesthesia.

Br J Anaesth 2000; **84**: 169–73

Keywords: analgesics opioid, remifentanil; anaesthetics volatile, isoflurane; anaesthetics i.v., propofol; surgery; abdominal; pain, postoperative

Accepted for publication: August 25, 1999

Remifentanil is a highly potent, selective µ-opioid receptor agonist belonging to the class of 4-anilidopiperidine derivatives.[1] The presence of an ester side chain allows rapid metabolism by non-specific esterases to remifentanil acid, which is approximately 4600 times less potent than remifentanil.[2] The terminal plasma half-life of remifentanil is 8–10 min and its context-sensitive time (i.e. biological half-life) is 3–5 min.[1] Hence, compared with other opioids, remifentanil can be continued to provide profound analgesia until the end of surgery without compromising recovery.[1 3–6]

However, because of the rapid offset of remifentanil, measures must be taken to provide analgesia for immediate postoperative pain relief. Four studies have examined postoperative pain control with the option of continuing remifentanil infusion at a reduced rate in the immediate postoperative period.[4–7] However, because of inter-individual variability in analgesic and respiratory responses to opioids, the use of remifentanil during recovery has been shown to require careful titration and monitoring.

An alternative approach is to administer an i.v. analgesic dose of a longer-acting opioid during operation, before discontinuing remifentanil anaesthesia. Two controlled studies[8 9] have evaluated postoperative pain control using morphine and/or approximately equipotent doses of fentanyl, buprenorphine and piritramide, given 20–25 min before the end of remifentanil-based anaesthesia followed by a further dose(s) of the opioid before transfer to routine analgesia. The intraoperative analgesic doses in both studies appeared inadequate as ≤50% of patients had none or mild pain during early recovery

In this study, we have compared the effects of morphine and fentanyl in doses expected to provide good postoperative analgesia on recovery when given near the end of anaesthesia involving remifentanil with isoflurane or propofol.

Patients and methods

This controlled, parallel group study was conducted at 52 centres in 14 countries, and coordinated and analysed centrally; treatment randomizations were computer-generated centrally. After obtaining approval from the Ethics

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Committee and written informed consent, we studied patients aged ≥18 yr, ASA I–III, undergoing elective, major abdominal, non-laparoscopic surgery of at least 60 min duration. Patients were excluded if they had a history of significant arrhythmia, uncontrolled hypertension (diastolic arterial pressure (DAP) >100 mm Hg), or severe or uncontrolled disease; were chronically receiving opioids, benzodiazepines, anticonvulsants, alpha$_2$-adrenoceptor agonists or had received these agents (excluding the use of a short-acting benzodiazepine for night sedation) 12 h before surgery; had received an investigational agent in the 12 weeks before the study; were more than 100% of ideal body weight; or were hypersensitive to opioids.

Midazolam was given as premedication. Induction of anaesthesia commenced with a slow (30–60 s) i.v. bolus dose of remifentanil 1 μg kg^{-1} and continuous infusion of 0.5 μg kg^{-1} min^{-1} followed by propofol, initially at 0.5 mg kg^{-1} and then 10 mg every 10 s to loss of consciousness. Propofol was started at 100 μg kg^{-1} min^{-1} for patients receiving remifentanil and propofol anaesthesia. The trachea was intubated after neuromuscular block with an agent used routinely at each centre. Patients receiving remifentanil–isoflurane anaesthesia underwent ventilation with an initial end-tidal concentration of 0.6% isoflurane (0.5 MAC) in oxygen–air; patients receiving propofol underwent ventilation with oxygen–air. Oxygen saturation and $P\text{E}'_{\text{CO}_2}$ were maintained at 94–99% and 4.66–5.86 kPa, respectively. Five minutes after intubation of the trachea, remifentanil infusion was reduced to 0.25 μg kg^{-1} min^{-1}.

Responses to intubation, skin incision, skin closure and intraoperative surgical stimuli were recorded and, where necessary, were treated with remifentanil bolus doses of 1 μg kg^{-1} or up to 100% increase in its infusion rate (maximum 2 μg kg^{-1} min^{-1}), or both. If this failed, isoflurane was increased by up to 0.5% end-tidal or the propofol infusion increased by up to 50 μg kg^{-1} min^{-1} in the respective anaesthesia groups. If these failed for either anaesthesia group, propofol 10–20 mg was given. Intraoperative bradycardia was managed with an anticholinergic agent and hypotension using i.v. fluids or vasopressor/anticholinergic agents.

Twenty-five minutes before the end of surgery, patients received an i.v. dose of morphine 15 mg or fentanyl 0.15 mg in a randomized manner, which had been prepared and blinded by the hospital pharmacy. A second (also blinded) reduced i.v. dose of the respective opioid (morphine 7 mg, fentanyl 0.05 mg) was administered during recovery if patients reported moderate or severe pain. At the end of surgery, propofol, isoflurane and remifentanil were switched off and residual neuromuscular block was antagonized if necessary. On resumption of spontaneous respiration, the trachea was extubated, and observations were continued in the recovery area.

Postoperative assessments

SAP, DAP, HR and Aldrete scores[10] were recorded at 1, 3, 5, 7 and 10 min after terminating anaesthesia and then every 5 min until extubation. An Aldrete score ≥9 signified recovery of physical, mental and physiological function to almost pre-anaesthetic levels. In addition, times to spontaneous respiration, adequate respiration (ventilatory frequency >8 bpm or $P\text{E}'_{\text{CO}_2}$ <6.66 kPa, or both), extubation, response to verbal commands (opening of eyes, lifting of limb) and the first Aldrete score ≥9 were recorded.

After extubation, the above variables and pain scores (at rest) using a verbal rating scale (0=none; 1=mild; 2=moderate; 3=severe) were recorded every 5 min for 60 min and thereafter every 15 min until discharge to the ward. Time of administration of the second i.v. dose of the study opioid was also recorded. Patients were deemed to qualify for recovery room discharge when two consecutive Aldrete scores of 9 or 10 were obtained, and pain, nausea and vomiting were adequately controlled. Times to qualification for and actual recovery room discharge were recorded. The occurrence of adverse events was monitored throughout the study and for up to 24 h after the end of anaesthesia. An adverse event was defined as any untoward medical occurrence experienced by the patient.

Data analysis

The study was powered on the time to extubation. Assuming an SD of 0.7 (log transformed data), 232 patients per group were estimated to provide 80% power to detect a difference of 20% in the time to extubation between the remifentanil–propofol and remifentanil–isoflurane groups at a two-sided 5% level.

Patient data and baseline characteristics in all four groups were analysed using one-way analysis of variance and a chi-square test. The primary efficacy end-point (time to extubation) was analysed using analysis of variance on log transformed data. A fixed effects two-way ANOVA was applied to simultaneously test for concurrent anaesthetic and the intraoperative blinded analgesic regimen of morphine or fentanyl. This methodology was also applied to the secondary end-points (i.e. time to spontaneous and adequate respiration, time to response to verbal command, time to first Aldrete score >9) to time the second dose of study opioid and actual discharge times from the recovery room. The proportion of patients with at least one response to intubation and skin incision was compared between concurrent anaesthetic groups using Fisher's exact two-tailed test. The number of treated responses to surgical stress, incidences or none or mild pain scores at Aldrete scores >9 and at recovery room discharge eligibility were compared between the four groups using Pearson chi-square two-tailed tests.

Pain scores were grouped in 5-min intervals from the end of anaesthesia. The maximum pain score within each time interval was selected and the percentage of patients with none or mild pain in the four treatment groups was calculated. Scatter plots of the derived summary data were reviewed and a cubic regression model was chosen to smooth the score patterns. For statistical comparison, the

Table 1 Patient characteristics and type and duration of anaesthesia in the two treatment groups after fentanyl or morphine for postoperative pain (median (range) or number)

	Remifentanil – isoflurane group		**Remifentani – propofol group**	
	Fentanyl	**Morphine**	**Fentanyl**	**Morphine**
n	137	142	136	138
Sex (M/F)	41/96	43/99	34/102	38/100
Age (yr)	51 2 (22 1–88 3)	53 6 (22 4–79.7)	52 5 (22 6–84.6)	52 2 (24 1–83.1)
Weight (kg)	70 5 (47 0–115 0)	70 0 (46.0–118 0)	71 0 (40 0–120 0)	70 0 (45 5–105 0)
ASA status (%)				
(1/11/111)	43/51/6	41/51/8	41/53/6	42/52/6
Surgical procedure (%)				
Abdominal	43	49	47	46
Urogenital	57	51	53	54
Anaesthesia duration (min)	132 (50–399)	124 (53–380)	131 (42–478)	120 (46–340)

proportion of none–mild pain scores to the total number of scores recorded by each patient was calculated. The averages of this derived variable were compared between the four treatment regimens using a one-way ANOVA model. To interpret the overall one-way ANOVA statistical test result, Bonferroni's test was used as a multiple comparison test to indicate significant group mean differences at an α level of 0.05.

Results

We studied 553 patients: 279 received remifentanil–isoflurane and 274 remifentanil–propofol anaesthesia. Two patients in the former group were withdrawn because of intraoperative complications. Thus 277 patients in the isoflurane group and 274 in the propofol anaesthesia group were included for efficacy analysis. Irrespective of the type of anaesthesia or the long-acting opioid(s) administered, the treatment groups were well matched for patient characteristics, ASA status, surgery type and anaesthesia duration (Table 1).

A significantly greater number of patients receiving remifentanil–isoflurane anaesthesia responded to tracheal intubation (7.6% *vs* 4.4%; $P<0.05$) and skin incision (15.5% *vs* 10.9%; $P<0.05$) compared with those in the remifentanil–propofol anaesthesia group. Proportions of patients responding to intraoperative surgical stimuli were similar for the two groups (isoflurane 66% *vs* propofol 57%).

Median times to extubation, spontaneous respiration, adequate respiration, response to verbal commands and Aldrete score ⩾9 were significantly longer for patients receiving remifentanil–propofol anaesthesia compared with those receiving remifentanil–isoflurane anaesthesia (Table 2).

At Aldrete scores ⩾9 (optimal point of recovery), 42–51% of patients had none or mild pain (Table 3). At this point, the proportion of patients reporting moderate pain was 24–33%, while those reporting severe pain was 21–26%. During recovery, 90–96% of patients received the second dose of morphine or fentanyl for moderate or severe pain within a median time of 21–26.5 min after the end of anaesthesia.

Table 4 shows the summary statistics of the proportion of none–mild postoperative pain scores to the total number of scores recorded by treatment regimen. Based on r^2 values (in Table 4) of the cubic regression for the different treatment groups, we conclude that the curve fit was better for patients receiving morphine compared with those receiving fentanyl. The cubic fit plots also indicate a higher percentage of patients receiving morphine with none or mild pain during the entire course of recovery from anaesthesia. The trend of significantly better postoperative analgesia with morphine than fentanyl was confirmed by ANOVA and *post hoc* tests comparing the means.

The incidence of adverse events was similar in all groups (Table 5). Muscle rigidity at induction occurred in 2–4% of patients. Hypotension and hypertension occurred most frequently during maintenance but the incidence was <1–2%. The most common adverse events during recovery were nausea (44–51%), vomiting (9–14%), shivering (8–10%) and hypertension (4–8%).

Postoperative respiratory depression or transient apnoea were reported in 13 (2.4%) patients and occurred at 27 min to >48 h after the end of anaesthesia. Respiratory depression was reported as a serious adverse event in two patients but was attributed to the use of morphine in only one patient. Overall, postoperative respiratory depression was mild or moderate and attributed to the long-acting opioids morphine or fentanyl in six of 11 patients.

Discussion

We have demonstrated that intraoperative administration of a longer-acting opioid before terminating remifentanil can provide immediate pain relief without severe effects on recovery times. Median times for extubation after terminating remifentanil anaesthesia were 9–11 min and were not different between groups. From this it can be concluded that late intraoperative administration of fentanyl or morphine does not severely affect postoperative recovery. However, at the doses and intraoperative administration schedules used, neither morphine nor fentanyl provided entirely adequate analgesia, particularly as only 42–51% of patients had none or mild pain but up to one-third of

Table 2 Median (25–75% quartiles) times for recovery variables after the end of anaesthesia in the two treatment groups after fentanyl or morphine for postoperative pain. **Significantly longer for propofol groups, $P < 0.01$

	Remifentanil – isoflurane group		**Remifentanil – propofol group**	
	Fentanyl (n = 135)	**Morphine (n = 142)**	**Fentanyl (n = 136)**	**Morphine (n = 138)**
Time to				
Extubation	10.0 (8.0–13.0)	9.0 (6.0–13.0)	11.0 (8.0–15.5)**	11.0 (8.0–15.0)**
Spontaneous respiration	8.0 (5.0–10.0)	6.0 (4.0–10.0)	8.0 (6.0–11.0)**	8.0 (5.0–12.0)**
Adequate respiration	9.0 (7.0–12.0)	9.0 (5.0–12.0)	11.0 (8.0–14.0)**	10.0 (7.0–14.0)**
Response to verbal command	8.0 (6.0–11.0)	7.0 (5.0–11.0)	10.0 (7.0–14.0)**	10.0 (6.0–13.0)**
Aldrete score ≥ 9	12.5 (8.0–19.0)	11.5 (8.0–18.0)	14.0 (10.0–27.5)**	15.0 (10.0–25.0)**

Table 3 Details of study opioid administration and pain scores after the end of anaesthesia in the two treatment groups after fentanyl or morphine for postoperative pain (median (25–75% quartiles) or number (%)). ***Significantly longer for propofol groups; $P < 0.001$ RR + Recovery room

	Remifentanil – isoflurane group		**Remifentanil – propofol group**	
	Fentanyl	**Morphine**	**Fentanyl**	**Morphine**
Patients receiving second opioid dose	129 (96)	128 (90)	130 (96)	124 (90)
Time to second opioid dose (min)	21.0 (16–29)	21.0 (15–28)	26.5*** (18–36)	24.0*** (18–36)
Pain score at Aldrete ≥ 9				
None–mild	65 (50)	61 (46)	54 (42)	65 (51)
Moderate	31 (24)	43 (33)	42 (33)	35 (28)
Severe	35 (26)	28 (21)	33 (25)	26 (21)
Patients with none–mild pain at RR discharge eligibility	94 (85)	114 (92)	98 (89)	106 (88)
Time to eligibility for RR discharge (min)	92 (60–137)	87 (55–133)	103 (64–138)	97 (55–141)
Time to actual RR discharge (min)	145 (90–230)	151 (103–205)	144 (94–246)	146 (93–234)

Table 4 Summary details on postoperative pain profiles in the two treatment groups after fentanyl or morphine. [a]One-way ANOVA $F = 4.724$ (df = 3); $P < 0.01$. *Mean difference significant at alpha level of 0.05

	Remifentanil – isoflurane group		**Remifentanil – propofol group**	
	Fentanyl	**Morphine**	**Fentanyl**	**Morphine**
Proportion of none–mild pain scores to total number of scores (mean (SD))[a]	0.48 (0.27)	0.59 (0.29)	0.52 (0.28)	0.59 (0.29)
95% Confidence interval	0.44–0.53	0.54–0.63	0.47–0.57	0.54–0.64
Bonferroni *post hoc* tests				
Mean difference				
Isoflurane + fentanyl	—	–0.103*	–0.035	–0.107*
Isoflurane + morphine	0.103*	—	0.068	–0.004
Propofol + fentanyl	0.035	–0.068	—	–0.072
Propofol + morphine	0.107*	0.004	0.072	—
r^2 cubic fit	0.77	0.90	0.69	0.91

Table 5 Occurrence of and most frequently reported adverse events in the two treatment groups after fentanyl or morphine for postoperative pain (number (%))

	Remifentanil – isoflurane group		**Remifentanil – propofol group**	
	Fentanyl (n = 137)	**Morphine (n = 142)**	**Fentanyl (n = 136)**	**Morphine (n = 138)**
Patients with adverse events reported	91 (66)	94 (66)	90 (66)	90 (65)
During induction				
Muscle rigidity	6 (4)	4 (3)	3 (2)	4 (3)
Hypotension	—	1 (<1)	1 (<1)	1 (<1)
During maintenance				
Hypotension	1 (<1)	2 (1)	2 (2)	2 (1)
Hypertension	2 (2)	1 (<1)	—	—
After surgery				
Muscle rigidity	—	—	2 (2)	2 (1)
Hypotension	1 (<1)	—	—	3 (2)
Hypertension	11 (8)	9 (6)	6 (4)	5 (4)
Shivering	14 (10)	12 (9)	11 (8)	12 (9)
Nausea	62 (45)	62 (44)	69 (51)	61 (44)
Vomiting	17 (12)	13 (9)	17 (13)	19 (14)

patients reported severe pain as they approached rapid orientation. Hence the second dose of the respective long-acting opioid included in the study to provide supplementary analgesia was required by almost all patients within 20–30 min of the end of anaesthesia. *Post hoc* analysis of analgesic efficacy showed that a significantly greater proportion of patients receiving morphine had none or mild pain during the period of recovery compared with fentanyl.

Overall, our observations resembled closely those reported by Albrecht and colleagues[8] who compared the effectiveness of approximately equipotent doses of morphine, fentanyl, piritramide and buprenorphine, given during operation to manage postoperative pain after remifentanil–propofol anaesthesia. In that study, median times to administration of the second opoid dose were similar (26–28 min). Recently, Sneyd[9] reported a controlled study on postoperative pain control in patients given morphine 0.2 mg kg^{-1} during remifentanil–isoflurane anaesthesia and compared pain scores with those who received fentanyl–isoflurane anaesthesia followed by routine postoperative analgesia. As in our study, approximately 50% of patients who received remifentanil anaesthesia had none or mild pain at 30 min after surgery and, with supplementary morphine, the proportion increased to approximately 90% at 2 h after surgery. More interestingly, patients in the conventional (isoflurane–fentanyl) anaesthesia–analgesia group also exhibited an almost identical level of pain control. Although no data were reported for proportions of patients with severe pain, the overall pattern of improvement in pain control during recovery room stay was similar to that observed in our study.

Although a significant proportion of patients experienced severe pain after operation, no patient reported this as an adverse event. Muscle rigidity at induction occurred in <4% of patients, reflecting the fast onset of remifentanil, particularly if the induction bolus dose had been given rapidly. The overall incidence of cardiovascular adverse events, specifically hypotension and bradycardia, was low which supported the use of a relatively small dose of isoflurane and propofol in this study.

Acknowledgements

The study was supported in part by a grant from Glaxo Wellcome. We are grateful to the following anaesthetists who generated the clinical data for the remifentanil international protocol USAB3116 and to Dr Marie-Christine Lauwers of Glaxo Wellcome, Belgium, for data management and statistical analysis

Remifentanil Study Group Investigators
Austria: Dr J. D. Engler, Leoben; Professor S Fitzal, Vienna; Professor G. Pauser, Salzburg. *Australia* Professor B. Baker, Camperdown, Dr A. Holloway, Brisbane; Dr R Molnar, Fitzroy *Belgium*· Professor H Adriaensen, Antwerp; Dr J.-L Demeere, Brussels; Dr F. Ernaelsteen, Charleroi; Dr P. Ewalenko, Brussels; Dr P Nokerman, Haine St Paul; Dr A. Stockman, Roeselare; Dr D. Van De Put, Aalst *Canada*. Dr P Fiset, Montreal, F. Fugère, Montreal; Dr C. D Mazer, Toronto, Dr C B. Warriner, Vancouver; Dr P Y. H Yu, New Westminster. *Denmark*. Dr N. E Drenck, Roskilde, Dr A. Horn, Copenhagen, Dr T Mogensen, Hvidovre, Dr C. Skovgaard, Glostrup *Finland* Dr S Kaukinen, Tampere; Dr M. Martikainen, Oulu; Dr M Oikkonen, Helsinki *Germany* Dr B Mackensen, Dr M Hautkappe, Dr J. Groh, Munchen; Dr D. Kuhn. Giessen; Dr K. F Rothe, Dresden; Dr H. C. Wartenberg, Bonn. *Ireland*. Dr K O'Sullivan, Dublin *Italy*: Dr P De Bellis, Professor S. Ischia, Verona, Professor C Launo, Genova, Dr B. Panascia. *Netherlands* Dr C L. G Rutten, Zwolle *Norway*: Dr O. Holgersen, Kristiansand. *Portugal* Dr M. M. Botelho, Lisbon, Dr C. De Miranda, Aveiro, Dr J. Moreira, Almada, Dr S. Quintal, Lisbon. *Spain* Dr J M. Campos, Barcelona, Dr L M Torres Morera, Cadiz. *Sweden*: Dr U. Bostrom, Dr J. Israelsson, Pitea, Dr M Brattwal, Dr C. Larson, Mólndal; Dr S. Martinsson, Kungalv; Dr E. Nordenskjold, Skovde; Dr S. Skold, Karlstad.

References

1 Glass PSA, Hardman D, Kamiyama Y, *et al.* Preliminary pharmacokinetics and pharmacodynamics of an ultra short acting opioid: remifentanil (GI87084B). *Anesth Analg* 1993; **77**: 1031–40

2 Kapila A, Glass PSA, Jacobs JR, *et al.* Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 1995, **83**: 968–75

3 Cartwright DP, Kvalsvik O, Cassuto J, *et al.* A randomized, blind comparison of remifentanil and alfentanil during anesthesia for outpatient surgery. *Anesth Analg* 1997; **85**: 1014–19

4 Bowdle TA, Camporesi EM, Maysick L, *et al.* A multicenter evaluation of remifentanil for early postoperative analgesia. *Anesth Analg* 1996; **83**: 1292–7

5 Yarmush J, D'Angelo R, Kirkhart B, *et al.* A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol *Anesthesiology* 1997; **87**: 235–43

6 Witkowski T, Azad S, Lessin J, *et al.* Post-op analgesia with remifentanil: dosage and side effects. *Anesth Analg* 1995; **80**: S554

7 Schuttler J, Albrecht S, Breivik H, *et al.* A comparison of remifentanil and alfentanil in patients undergoing major abdominal surgery. *Anaesthesia* 1997; **52**: 307–17

8 Albrecht S, Schüttler J, Fechner J, *et al.* Postoperative pain management following remifentanil-based anesthesia for major abdominal surgery *Anesth Analg* 1998; **86**: S253

9 Sneyd JR. Morphine before the termination of remifentanil provides effective transition to routine analgesia following major surgery: A comparison with current practice. *Br J Anaesth* 1998; **80**: A614

10 Aldrete JA, Kroulik D. A post anesthetic recovery score. *Anesth Analg* 1970; **49**: 924–33

British Journal of Anaesthesia **84** (2): 174–8 (2000)

Comparison of the incidence of complications at induction and emergence in infants receiving oral atropine *vs* no premedication

C. A. Shaw[1]*, A. A. Kelleher[2], C. P. Gill[1 5], L. J. Murdoch[4], R. H. Stables[3] and A. E. Black[1]

[1]Department of Anaesthesia, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, UK. [2]Department of Anaesthesia and [3]Clinical Trials Unit, Royal Brompton Hospital NHS Trust, London, UK. [4]Department of Anaesthesia, St George's Hospital Healthcare NHS Trust, London, UK

Present address: [5]Hillingdon Hospital NHS Trust, Middlesex, UK

**Corresponding author*

We studied 120 patients less than 1 yr of age, allocated randomly to receive atropine 40 $\mu g\ kg^{-1}$ orally 1 h before operation (group A) or no premedication (group B). All patients underwent a standardized anaesthetic, including inhalation induction with halothane followed by atracurium 0.5 mg kg^{-1}, tracheal intubation and positive pressure ventilation. Monitoring during anaesthesia included heart rate, arterial oxygen saturation, temperature and airway conditions at induction and emergence. The incidence of a decrease in arterial oxygen saturation to 94% or less at induction and recovery was similar in both groups (30.5% at induction, 39% at extubation in group A; 31% at induction, 41% at extubation in group B). There were significantly more airway complications in group B both at induction and emergence (25% and 49%, respectively, compared with 9% and 25% in group A; $P<0.015$). Mean heart rate at induction and in the peroperative period was significantly higher in the group receiving atropine ($P \leq 0.001$). There was an increased incidence of bradycardia (decrease in heart rate of ≥20%) at induction in the non-premedicated group (23% in group B compared with 10% in group A), but this was not statistically significant. We conclude that the incidence of airway complications at induction and emergence was reduced by orally administered atropine premedication.

Br J Anaesth 2000; **84**: 174–8

Keywords: premedication, atropine; anaesthesia, paediatric; infants; airway, complications

Accepted for publication: September 28, 1999

Since the days of ether and chloroform, anticholinergic drugs have been used as an adjunct to anaesthesia to reduce potentially troublesome airway secretions and prevent excessive vagal activity. With the advent of less irritant inhalation agents, this practice has been called into question, and as long ago as 1962 it was suggested that anticholinergic premedication in adults was unnecessary.[1 2] Indeed, anticholinergic drugs are now rarely prescribed for adults before operation.[3]

It is widely accepted that children, although possibly not neonates,[4] have higher vagal tone than adults, resulting in potentially more severe adverse airway and cardiac events associated with anaesthesia.[5–7] This has resulted in many institutions routinely prescribing atropine as premedication to infants and children. Although this is safe practice,[8] it may be unpleasant for the patient, causing dry mouth, pyrexia and tachycardia. Furthermore, tachycardia may make subsequent assessment of volaemic status and adequacy of anaesthesia difficult.[9]

Although the practice of premedication with atropine in young children is widespread it is certainly not universal and its value has been questioned recently.[10] Paediatric anaesthetists who do not routinely prescribe atropine premedication have not reported an increased incidence of severe adverse sequelae.[10 11] Our study was undertaken in two centres by anaesthetists with a regular commitment to paediatric anaesthesia. The aim was to determine whether atropine is still appropriate as premedication in infants or whether this practice may now be safely abandoned as it has been in adults. We studied the effect of atropine given as an oral premedicant in neonates and infants on the incidence of complications on induction and emergence.

Patients and methods

An initial pilot study was performed on 20 patients. The subsequent power analysis indicated a minimum sample size of 94 to detect a 5% difference in arterial oxygen saturation at 80% power. After obtaining approval from the Ethics Committee and informed written parental consent, we studied 120 patients less than 1 yr of age, allocated randomly (using a random number generator) to receive

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

atropine 40 μg kg^{-1} orally, 1 h before operation (group A) or no premedication (group B). The study was carried out at two centres, Great Ormond Street Hospital for Children and St George's Hospital, London, UK. All patients were ASA I or II undergoing elective surgery which required tracheal intubation as part of the anaesthetic technique. Exclusion criteria were emergency surgery, significant cardiovascular or respiratory instability, pyrexia greater than 38°C, narrow angle glaucoma, atropine hypersensitivity and autonomic imbalance. Patients undergoing neurosurgical procedures and those with a history of previous airway problems during anaesthesia were also excluded. At the time of the preoperative anaesthetic assessment on the ward, heart rate and temperature were recorded.

Inhalation induction was used with incremental halothane (up to 5%) in oxygen (minimum $F\text{I}_{O_2}$ 0.3) and nitrous oxide using a hand-held Ayre's T-piece (Jackson–Rees modification). As soon as anaesthesia was achieved, i.v. access was obtained and tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with halothane in oxygen (minimum $F\text{I}_{O_2}$ 0.3) and nitrous oxide. Appropriate halothane concentrations were used according to clinical signs of depth of anaesthesia. Positive pressure ventilation to normocapnia was provided by a Nuffield Penlon 200 ventilator, with Newton valve attachment, via an Ayre's T-piece. Analgesia was provided as appropriate using a combination of local anaesthesia, simple analgesic suppositories and opioid analgesics.

In addition to the standard monitoring used continuously throughout anaesthesia, a trained observer, unaware of the patient's premedication group, recorded the minimum heart rate achieved at any point during induction and in the peroperative period, maximum peroperative rectal temperature and minimum arterial oxygen saturation achieved at induction, in the peroperative period and at extubation. The pulse oximeter was an Ohmeda Biox 3740 and soft probe 8123-009 with an averaging time of 6 s and a pulse interval of 12 s. The anaesthetist, who was also blinded to the randomization, noted airway conditions at induction and extubation. Airway conditions assessed were: excessive secretions, breath- holding, cough and laryngospasm. Excessive secretions were defined as requiring application of more than one suction to see the larynx and achieve tracheal intubation. Breath-holding was defined as cessation of a regular breathing pattern during induction of, or emergence from, anaesthesia. The perioperative use of succinylcholine or atropine was also noted. At the end of surgery, neuromuscular block was antagonized with neostigmine 50 μg kg^{-1} and atropine 25 μg kg^{-1}. The oropharynx was suctioned as routine and extubation was performed when the patient was breathing regularly and awake, and with airway reflexes fully restored.

All statistical tests were performed using the software SPSS for windows release 6.1.3 (Dec. 95). Data on normally distributed variables are presented as mean (SD). Comparison of these means was performed using a two-tailed Student's *t* test for unpaired observations. Differences in proportions were compared by chi-square methodology. Statistical significance was indicated by $P \leq 0.05$. The association between a range of baseline characteristics and the occurrence of an outcome event was examined using a multiple logistic regression with forward stepwise methodology

Table 1 Patient characteristics, surgical presentation and anaesthetic details in group A (atropine premedication) and group B (no premedication) Data are mean (SD) [range] or number *$P<0.05$ compared with group A

	Group A (atropine) (*n* = 59)	**Group B (no premed) (*n* = 61)**
Age (days)	111 [1–336]	127 [2–308]
Weight (kg)	5.4 (1.9) [2.1–9.8]	4.6 (2.4) [1.7–11.0]
Sex (M/F)	36/23	40/21
No ≤36 weeks' gestation	9	14
No ≤5 kg	26	31
Surgical procedure (*n*)		
General/urology/orthopaedic	38	41
Cleft lip/head and neck	13	11
Ophthalmic	8	9
Operation time (min)	70 (44)	54 (36)*
Peroperative temperature (°C)	36.7 (0.7)	36.6 (0.6)
Peroperative heart rate (beat min^{-1})	146 (18)	128 (20)
$F\text{I}_{O_2}$	0.62 (0.31)	0.66 (0.31)
Succinylcholine at induction (*n*)	9	10
Atropine on induction (*n*)	3	4
Intraoperative atropine (*n*)	3	0

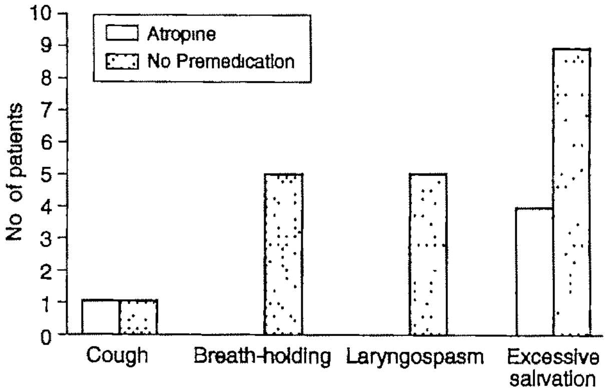


Fig 1 Airway complications on induction in patients premedicated with atropine and in those who received no premedication

Results

Patient characteristics in the two groups were similar (Table 1), except for duration of operation which was significantly longer in the group who received atropine (group A), despite randomization.

Figure 1 illustrates the distribution of airway complications at induction between the two groups. These were more common in patients who did not receive premedication. Fifteen (24.6%) patients in group B compared with five (8.5%) in group A had one or more of the four complications (laryngospasm, cough, excessive secretions and breath-holding) ($P \leq 0.015$).

Table 2 Changes in heart rate and arterial oxygen saturation in group A (atropine premedication) and group B (no premedication). Data are mean (SD) [percentage change] ***$P<0.001$

	Group A (atropine) (n = 59)	**Group B (no premed) (n = 61)**
Change in heart rate on induction (beat per min^{-1})	+14 (28)*** [+12%]	−10 (28)*** [−7%]
Change in peroperative heart rate (beat min^{-1})	+15 (22)*** [+13%]	−1 (25)*** [+0 2%]
Decrease in heart rate >20% (n)	6 [10%]	14 [23%]
No. of patients with $S\text{P}_{\text{O}_2}$ <94% on induction	18 [30.5%]	19 31%]
Minimum $S\text{P}_{\text{O}_2}$ on induction	86%	50%
No of patients with $S\text{P}_{\text{O}_2}$ <94% on extubation	23 [39%]	25 [41%]
Minimum $S\text{P}_{\text{O}_2}$ on extubation	50%	60%

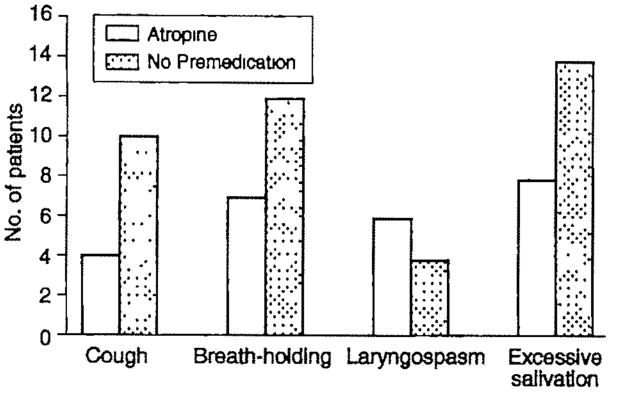


Fig 2 Airway complications on extubation in patients premedicated with atropine and in those who received no premedication.

Six (10%) patients in the group who received atropine and 14 (23%) in the unpremedicated group showed a decrease in heart rate of more than 20% at induction compared with the preoperative resting heart rate; this was not statistically significant. Mean heart rate increased compared with the resting preoperative observations both at induction (by 14 beat min^{-1}) and in the peroperative period (by 15 beat min^{-1}) in group A. Infants in group B demonstrated little change in mean heart rate (Table 2). This difference between groups was significant ($P \leq 0.001$).

There was no significant difference between groups in the number of patients with oxygen saturations less than 94%, or in the minimum arterial oxygen saturation at induction. The most profound desaturations on induction occurred in the unpremedicated group.

At emergence, airway complications occurred more commonly in group B, with 30 (49.2%) compared with 15 (25.4%) patients in group A having one or more of the four complications ($P \leq 0.006$). The type of airway complications seen on extubation in the two groups is shown in Figure 2.

There was no difference between groups in the number of patients with arterial oxygen saturations less than 94% or in the minimum arterial oxygen saturation at extubation (Table 2).

To examine the factors associated with an airway complication, a forward step multiple logistic regression analysis was performed. The following variables were entered into the analysis: operation type (three categories shown in Table 1); duration of operation; sex; gestational age at delivery (greater or less than 36 weeks); weight; use of additional atropine at induction or in the peroperative period; and use of succinylcholine at induction. This secondary analysis showed that the occurrence of airway complications at induction was associated with lower patient weight and the use of succinylcholine. At extubation, the occurrence of airway complications was associated with lower patient weight and gestational age at birth. Duration of operation was not associated with airway complications at either induction or extubation using this form of secondary analysis.

Discussion

In this study, performed by anaesthetists with a regular paediatric commitment, the incidence of complications was comparable with previous studies; approximately 30% and 40% of patients had arterial oxygen saturations of 94% or less at induction and extubation, respectively. These finding are similar to those of Laycock and McNicol[12] who found that during induction of anaesthesia, 40% of children less than 1 yr had arterial oxygen saturations of 90% or less, whereas Kong and colleagues[13] found that 27% of their patients (neonates and small infants weighing less than 5 kg) had decreases in arterial oxygen saturation of more than 5% from preoperative values during inhalation induction. Kong's group also showed that there was a significantly higher incidence of patient arterial desaturations when anaesthesia was performed by less experienced anaesthetists. It is possible that the incidence of complications in paediatric patients may be greater with less experienced anaesthetists and that in such circumstances atropine premedication affords a greater margin of safety.

Several routes of administration and doses of atropine are available. The dose chosen for this study was 40 μg kg^{-1} orally, 1 h before operation, to reflect current practice in our hospitals. A study by Crean and colleagues[6] compared atropine 40 μg kg^{-1} orally with 20 μg kg^{-1} i.m. and found no significant difference between the two doses, methods of administration or clinical effect. More recent work by Gervais and colleagues[14] has demonstrated variable cholinoceptor occupancy after both oral and i.m. administration. Other workers have found similar clinical effects and serum atropine concentrations after oral, i.m. and i.v. atropine administration.[15 16]

We compared oral atropine with no premedication to reflect local practice. Although most clinicians and nursing staff prefer to avoid the i.m. route, one survey suggests that parental objection is rare.[17] There were significantly more airway complications in group B both at induction and emergence. Excessive salivation was the most common problem (Figs 1, 2), and occurred both as a sole complication and in association with the other airway complications studied. It is difficult to accurately quantify the presence of excessive secretions and we considered the requirement of more than one application of suction to clearly see the larynx and achieve intubation as excessive. Some anaesthetists argue that airway secretions rarely lead to serious sequelae and do not warrant routine premedication with atropine.[10 11] We were unable to demonstrate significantly more episodes of arterial oxygen desaturation or bradycardia as a result of airway complications and attribute this to swift, appropriate airway management by experienced anaesthetists. Although the study did not dictate inspired oxygen content ($F\text{I}_{\text{O}_2}$), there was no difference between groups in $F\text{I}_{\text{O}_2}$ (Table 1). Rapid intervention was allowed at the first sign of complications, and a few patients in each group required administration of succinylcholine and atropine (Table 1).

We suggest that serious sequelae could arise with less experienced anaesthetists. The three patients with severe arterial desaturations less than 70% at induction were all in group B, and two of the three were associated with excessive secretions. At emergence, eight patients had arterial oxygen saturations less than 80%; three of these were associated with excessive secretions and the remaining five were associated with one or more of the other three airway complications studied.

Mean difference in heart rate at induction compared with the peroperative period differed between the two groups, with patients in group A demonstrating increases of 14 and 15 beat min^{-1} compared with little change in group B. Although highly statistically significant ($P \leqslant 0.001$), this mean increase in heart rate is unlikely to be clinically important. More interesting, however, was the fact that twice as many unpremedicated than premedicated patients had a decrease in heart rate of more than 20% at induction (Table 2). The most serious decreases in heart rate were associated with airway complications.

Secondary analysis by forward step multiple logistic regression indicated that the occurrence of airway complications at induction and emergence was associated with low patient weight. This is unsurprising. Although it would be interesting to examine this group further, the number of patients weighing less than 5 kg and suitable for this study was, unfortunately, small.

Halothane has for many years been the agent of choice for inhalation induction of anaesthesia in children. However, sevoflurane has recently gained in popularity. Despite this, as recently as 1998 the Association of Paediatric Anaesthetists of Great Britain and Ireland overwhelmingly rejected a motion proposing the replacement of halothane by sevoflurane. This was partly on the grounds of cost, but it was also noted that the longer duration of action of halothane might confer distinct advantages over sevoflurane, particularly during airway procedures.[18] Thus it is likely that halothane will not be completely replaced by sevoflurane for inhalation induction of anaesthesia in the foreseeable future. We believe that atropine premedication will continue to serve a useful role in inhalation induction of anaesthesia of infants and children.

In summary, we found that although airway complications occurred in both groups, the incidence was significantly lower, both at induction and extubation, in the group who received atropine premedication.

References

1 Holt AT, Cornell MD. Premedication with atropine should not be routine. *Lancet* 1962; **ii**: 984–5

2 Eger EI. Atropine, scopolomine, and related compounds. *Anesthesiology* 1962; **23**: 365–83

3 Mirakhur RK, Clarke RSJ, Dundee JW, McDonald JR. Anticholinergic drugs in anaesthesia. A survey of their present position. *Anaesthesia* 1978; **33**: 133–8

4 Robinson S. *Pediatric Anaesthesia, vol. I* Edinburgh: Churchill Livingstone, 1983

5 Barash PG, Glanz S, Katz JD, Taunt K, Talner NS. Ventricular function in children during halothane anesthesia. *Anesthesiology* 1978; **49**: 79–85

6 Crean PM, Laird CRD, Keilty SR, Black GW. The influence of atropine premedication on the induction of anaesthesia with isoflurane in children. *Paediatr Anaesth* 1991; **1**: 37–9

7 Sagarminaga J, Wynands JE. Atropine and the electrical activity of the heart during induction of anaesthesia in children. *Can Anaesth Soc J* 1963; **10**: 328–30

8 Arthurs GJ, Davies R. Atropine—a safe drug. *Anaesthesia* 1980; **35**: 1077–9

9 Murray DT, Forbes RB, Dillman JB. Haemodynamic effects of atropine during halothane or isoflurane anaesthesia in infants and small children. *Can J Anaesth* 1989; **36**: 295–300

10 Johr M. Is it time to question the routine use of anticholinergic agents in paediatric anaesthesia? *Paediatr Anaesth* 1999; **9**: 99–101

11 Parnis SJ, Van de Walt JH. A national survey of atropine use by Australian anaesthetists. *Anaesth Intensive Care* 1994; **22**: 61–5

12 Laycock GJA, McNicol LR. Hypoxaemia during induction of anaesthesia—an audit of children who underwent general anaesthesia for routine elective surgery. *Anaesthesia* 1988, **43**: 981–4

13 Kong AS, Brennan L, Bingham R, Morgan Hughes J. An audit of induction of anaesthesia in neonates and small infants using pulse oximetry. *Anaesthesia* 1992; **47**: 896–9

14 Gervais HW, El Gindi M, Radermacher PR, Voltzang C, Palm O, Duda D. Plasma concentration following oral and intramuscular atropine in children and their clinical effects. *Paediatr Anaesth* 1997; **7**: 13–18

15 Wark HJ, Overton JH, Marian P. The safety of atropine premedication in children with Down's syndrome. *Anaesthesia* 1983; **38**: 871–4

16 Saarnivaara L, Kautto UM, Iisalo E, Pihlajamaki K. Comparison of pharmocokinetic and pharmacodynamic parameters following oral or intramuscular atropine in children. Atropine overdose in two small children. *Acta Anaesthesiol Scand* 1985; **29**: 529–36

17 Parnass SM, Pittman SK, Horitz HA, McCarthy RJ. A survey of parental attitudes following pediatric anesthesia at a community hospital. *Anesthesiology* 1993; **79**: A1156

18 Hatch DJ. New inhalational agents in paediatric anaesthesia. *Br J Anaesth* 1999; **83**: 42–9

British Journal of Anaesthesia **84** (2) 179–82 (2000)

Anaesthetic complications of acromegaly

P. A. Seidman[1]*, W. A. Kofke[1], R. Policare and M. Young

Department of Anesthesiology, CCM University of Pittsburgh Medical Center, Pittsburgh, PA 15261, USA

[1]Present address: West Virginia University, Department of Anesthesiology, 3618 HSC, PO Box 9134, Morgantown, WV 26506–9134, USA

**Corresponding author*

The anaesthetic risks of acromegaly include difficulties in airway management, hypertension, and cardiac, gastrointestinal and renal problems. To estimate the incidence of major complications in this rare group of patients, we reviewed 28 patients with acromegaly who had pituitary tumour excision over a 10-yr period. Each patient was matched for age, weight and sex to a non-acromegalic patient undergoing transsphenoidal pituitary surgery. Acromegalic patients received significantly more fentanyl and midazolam and less thiopental and succinylcholine than controls (all $P<0.05$). Mean arterial pressure (baseline, minimal and maximal values) was higher in acromegalic patients than in controls. There was no difference between groups in the use of vasoactive drugs. Pa_{O_2}, FI_{O_2} and Pa_{CO_2} were similar in both groups. Arterial pH was significantly lower ($P=0.015$), blood glucose was higher ($P<0.001$) and fluid intake minus output was higher ($P=0.04$) in acromegalic patients than in controls. Airway difficulty and tongue enlargement were encountered more often in acromegalic patients ($P=0.002$ and $P=0.01$, respectively). Our data confirm that in acromegalic patients: airway difficulties occurred more frequently; severe haemodynamic instability did not typically occur during surgery for acromegaly, pulmonary gas exchange was not altered during operation; glucose intolerance may be an intraoperative problem; and fluid regulation may be altered.

Br J Anaesth 2000; **84**: 179–82

Keywords: complications, acromegaly; surgery, neurological

Accepted for publication. September 27, 1999

Acromegaly has been recognized since ancient times[1] and was described as a distinct clinical syndrome by Marie[2] in 1886. The aetiology of the disorder was identified as pituitary dysfunction by Cushing in 1909.[3] The constellation of features is well described and encompasses almost all major organ systems.[4 5] Previous anaesthetic studies have focused specifically on airway difficulty during induction in patients with acromegaly.[6–15] Acromegaly has also been associated with diabetes,[4 5 16] cardiovascular disorders,[17–19] pulmonary dysfunction[20] and myopathy.[21] No report has focused on overall anaesthetic morbidity involving these organ systems. The purpose of this retrospective study of acromegalic patients was to determine the incidence of difficulties in anaesthetic management associated with organ systems other than the airway, in addition to assessing airway-related morbidity.

Patients and methods

Approval for the study was obtained from the Institutional Review Board. Charts of patients with acromegaly who had transsphenoidal pituitary tumour excision over a 10-yr period were examined for evidence of preoperative hypertension, diabetes and cardiomegaly, and patient sex, age and weight were recorded. Anaesthetic complications were noted, including: requirement for fibreoptic intubation; difficult intubation (defined as >1 laryngoscopy attempt); large tongue; airway difficulty; >20% change in arterial pressure or heart rate; and ability to extubate the trachea in the operating room. The anaesthetic agents used were detailed. Arterial pressure variables recorded included systolic, diastolic and mean arterial pressures. Initial, minimal and maximal arterial pressures and heart rate readings were noted for each patient. In addition, blood glucose and fluid intake and output were recorded.

The 28 acromegalic patients were compared with 28 control patients matched for age, sex and weight, all of whom underwent transsphenoidal pituitary resection surgery but did not have acromegaly.

Statistical analysis

For dichotomous variables, McNemar's test for correlated proportions was used.[22] These variables included: hyperten-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Baseline values for physical characteristics (mean (SEM) or range) and pathological problems (number of patients). *$P < 0.05$ between groups

Group	Weight (kg)	Age (yr)	Sex (M/F)	Hypertension*	Diabetes*	Cardiomegaly*
Acromegaly	95 (3.6)	45.2 (17–68)	15/13	15	9	5
Control	87 (3.2)	44.5 (20–66)	15/13	2	4	0
P	0.136	0.86		0.01	0.03	0.04

Table 2 Anaesthetic complications and intraoperative monitoring (mean (SEM) or number)

	n	Fibreoptic intubation	Difficult intubation	Enlarged tongue	Airway difficulty	Haemodynamic changes (>20%)	Extubation in operating room
Acromegaly	28	3	12	19	11	12	20
Control	28	0	1	0	1	5	25
P		0.000	0.01	0.001	0.01	0.17	0.09

	$F_{I_{O_2}}$	pH	Pa_{O_2}	Pa_{CO_2}	Blood glucose (mmol litre^{-1})	Positive fluid balance (ml)
Acromegaly	0.34 (0.03)	7.44 (0.009)	16.7 (0.9)	4.5 (0.1)	12.4 (0.7)	1553 (18)
Control	0.45 (0.01)	7.47 (0.008)	18.9 (1.3)	4.1 (0.1)	9.6 (0.5)	1270 (119)
P	0.91	0.015	0.15	0.12	< 0.001	0.04

sion, diabetes and cardiomegaly (Table 1); anaesthetic complications (Table 2); and drugs used. Paired *t* tests were used for continuous variables that had five or more instances in both the control and acromegalic groups. Computations were performed using the SPSS for Windows statistical program[23] for weight and age (Table 1), metabolic and intraoperative pulmonary function ($Pa_{O_2}/Pa_{CO_2}/F_{I_{O_2}}$) and the quantities of drugs used.

Results

Pre-existing conditions are shown in Table 1. Patients with acromegaly had a higher incidence of preoperative hypertension (P=0.01), diabetes (P=0.03) and cardiomegaly (P=0.04).

Anaesthetic complications are listed in Table 2. Fibreoptic intubation was required in three of 28 acromegalic patients and none of the control patients. Acromegalic patients were more likely to have a difficult intubation (P=0.01), enlarged tongue (P=0.001) and airway difficulty (P=0.01). Although haemodynamic changes were not statistically significant between the two groups, there were more changes in the acromegalic patients than in controls (12 *vs* five). The incidence of extubation in the operating room was similar in both groups.

With respect to metabolic and pulmonary function, arterial pH was lower in acromegalic patients (mean pH 7.44 (SEM 0.009) *vs* 7.47 (0.008); P=0.015) with no differences in Pa_{O_2} or Pa_{CO_2}. Blood glucose was significantly higher in acromegalic patients (12.4 (0.7) *vs* 9.6 (0.5) mmol litre^{-1}) ($P<0.001$). Urine output was significantly lower in acromegalic patients ($P<0.001$) resulting in a greater positive fluid balance (1553 (118) *vs* 1270 (119) ml; P=0.04).

Haemodynamic changes during anaesthesia are shown in Figure 1. Acromegalic patients had significantly higher mean arterial pressures and heart rate at baseline compared with controls. Minimal and maximal arterial pressures recorded in acromegalic patients were higher than those in controls. There were no differences in minimal or maximal heart rates between groups. Larger absolute and weight-normalized doses of fentanyl (3.50 (0.20) *vs* 3.06 (0.10) μg kg^{-1}; P=0.05) and midazolam (0.07 (0.01) *vs* 0.04 (0.003) mg kg^{-1}; P=0.04) were used in the acromegalic patients compared with the controls. Absolute doses of thiopental and succinylcholine were similar, although doses of thiopental normalized for weight were lower in the acromegaly group (4.69 (0.24) *vs* 5.36 (0.21) mg kg^{-1}; P=0.04).

There were no significant differences between groups in the amount of vasoactive or anaesthetic drugs used during operation.

Discussion

Given the rarity of acromegaly, an investigation such as this might be expected to be retrospective. We made every effort to ensure that the control group provided a suitable comparison with the acromegaly group. Only patients undergoing a comparable surgical procedure were included and patients were matched for age, sex and weight. Control patients were selected on the first encounter in the database when noted to be the same age, sex and weight. Thus although we believe this to constitute a suitable control group, it is possible that other unaccounted factors were heterogeneously distributed in the control group. Such is the nature of retrospective studies. This also raises the issue of the suitability of performing statistical tests on this database. We elected to perform such analyses, cognisant of the potential problems, to better enable description and contrast of the two groups. Another issue with the retrospective design is inherent in the expectation, prior to this investigation, that acromegalic patients will have difficult airways to manage. Thus observed differences in

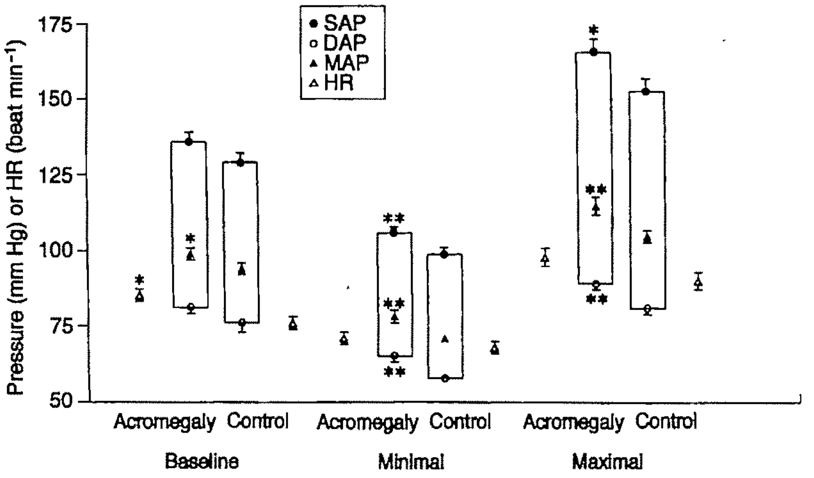


Fig 1 Physiological variables. Baseline, minimal and maximal values for heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures before and during operation. Values are mean (SEM); boxes indicate 25–75th percentiles and 'whiskers' the largest and smallest values. $^{*}P<0.05$, $^{**}P<0.01$ between groups

airway management may reflect a prospective bias in the neuroanaesthetists' practice.

Acromegaly involves oversecretion of growth hormone (GH) which can result from oversecretion of growth hormone releasing hormone (GHRH) from the hypothalamus or oversecretion of the hormone itself from a pituitary tumour. There are also a few malignant tumours that synthesize GH. Testing for blood concentrations of GH is important diagnostically, but the clinical manifestations are the same whatever the source. The incidence of acromegaly is approximately 3–4 per million per year, with a prevalence in the population of approximately 50–70 cases per million;[4] thus prospective studies are almost impossible to perform. Cases are equally distributed between the sexes and patients are usually diagnosed when aged 40–50 yr. The clinical manifestations include somatic changes in addition to local changes secondary to pituitary enlargement. The somatic changes are caused by the effects of GH on growth and on insulin metabolism. While the classic acromegalic facies is well known, the changes are so insidious that few patients seek treatment secondary to appearance changes. The symptoms of excess GH secretion often pre-date the changes from pituitary enlargement and include diabetes mellitus, hypertension, heart disease (including left ventricular hypertrophy, congestive heart failure and global cardiomegaly), osteoarthritis, amenorrhoea, skin tags, colonic polyps, hyperhydrosis, carpal tunnel syndrome and sleep apnoea. Acral enlargement leads to the familiar features of the acromegalic. The coarsening of features with bony proliferation can concomitantly involve macroglossia, prognathism with malocclusion and hypertrophy of the laryngeal soft tissue, epiglottis and aryepiglottic folds. The constellation of physical manifestations, especially heart and lung disease, combined with upper airway involvement, make these patients a particular concern to the anaesthetist. Because of the rarity of the disease, there may be a tendency to over or underestimate the potential problems.

Cardiac complications in acromegalic patients have been well described.[17–19] Acromegaly usually involves cardiac tissue and can occur with or without coexisting hypertension. The incidence and severity of cardiac hypertrophy relates to the duration of the disease, but there are no data to support a relationship between the degree of cardiac enlargement and GH concentrations.[17] Cardiomegaly was found to be disproportionate to other organ hypertrophy in a prospective study of autopsy data.[18] There is little evidence to support the notion that there is accelerated atherosclerosis in this population. There is a higher incidence of small vessel disease and lymphomononuclear infiltration than in the normal population but the significance of these findings is unclear.[18]

In our acromegalic study population, we observed a higher incidence of pre-existing hypertension and cardiomegaly. However, there was no evidence of a major effect during operation in terms of haemodynamic changes nor were there any differences between groups in the use of vasoactive drugs such as ephedrine or trimethaphan. None the less, arterial pressure was somewhat higher in patients with acromegaly, although this was not clinically significant.

When lung function is assessed in patients with an absence of associated cardiac complications, studies confirm that gas exchange in acromegalic patients is not grossly abnormal. Pulmonary function tests are consistent with extrathoracic obstruction as the cause of pulmonary complications. Flow–volume loops confirm greater impairment of expiration than inspiration.[20] The acral enlargement consistently involves upper airway redundancy, which includes pharyngeal and tracheal changes that can also lead to airway complications. This is consistent with the obstructive component seen in pulmonary function tests. Our data confirm that abnormalities in gas exchange are not a major problem in patients with acromegaly undergoing general anaesthesia.

Oversecretion of GH with acromegaly produces resistance to the effects of insulin, which leads to glucose intolerance.

This was noted in our patients, with blood glucose concentrations being significantly higher in acromegalic patients compared with controls. This finding may be important, as hyperglycaemia is known to worsen some types of cerebral ischaemia.[24] We also observed lower urine output in acromegalic patients, despite comparable i.v. fluid volumes during operation. Potential causes of these differences, relative to the control group, include preoperative hypovolaemia, lower cardiac output, fluid volume dysautoregulation and/or renal dysfunction. These data indicate mild intraoperative metabolic problems with acromegaly.

Our data support previous observations that airway difficulties are more common in patients with acromegaly. Preexisting cardiovascular problems are more frequent but, taken as a group, the extent of intraoperative changes in arterial pressure and heart rate were not major causes of morbidity during anaesthesia. Mild perioperative metabolic problems occur in acromegalic patients with respect to blood glucose and fluid balance.

References

1 Old Testament. *Samuel* **17**: 1–58

2 Marie P. On two cases of acromegaly. *Rev Med* 1886; **6**: 297–333

3 Cushing H. Partial hypophysectomy for acromegaly: with remarks on the function of the hypophysis. *Ann Surg* 1909; **50**: 1002–17

4 Melmed S. Acromegaly. *N Engl J Med* 1990; **322**: 966–77

5 Melmed S, Fagin J. Acromegaly update–etiology, diagnosis and management. *West J Med* 1987; **146**: 328–36

6 Hassan SZ, Matz GJ, Lawrence AM, Collins PA. Laryngeal stenosis in acromegaly: a possible cause of airway difficulties associated with anesthesia. *Anesth Analg* 1976; **55**: 57–60

7 Messick JM Jr, Laws ER Jr, Abboud CF. Anesthesia for transsphenoidal surgery of the hypophyseal region. *Anesth Analg* 1978; **57**: 206–15

8 Morewood DJ, Belchetz PE, Evans CC, Whitehouse GH. The extrathoracic airway in acromegaly. *Clin Radiol* 1986; **37**: 243–6

9 Kitahata LM. Airway difficulties associated with anaesthesia in acromegaly. Three case reports. *Br J Anaesth* 1971; **43**: 1187–90

10 Southwick JP, Katz J. Unusual airway difficulty in the acromegalic patient–indications for tracheostomy. *Anesthesiology* 1979; **51**: 72–3

11 Singelyn FJ, Scholtes JL. Airway obstruction in acromegaly: a method of prevention. *Anaesth Intensive Care* 1988; **16**: 491–2

12 Hakala P, Randell T, Valli H. Laryngoscopy and fibreoptic intubation in acromegalic patients. *Br J Anaesth* 1998; **80**: 345–7

13 Chan VWS, Tindal S. Anaesthesia for transsphenoidal surgery in a patient with extreme gigantism *Br J Anaesth* 1988; **60**: 464–8

14 Ovassapian A, Doka JC, Romsa DE. Acromegaly–use of fiberoptic laryngoscopy to avoid tracheostomy. *Anesthesiology* 1981; **54**: 429–30

15 Rees PJ, Hay JG, Webb JR. Acute exacerbation of upper airway obstruction in acromegaly. *Postgrad Med J* 1982; **58**: 429–30

16 Garcia-Estevez DA, Araujo-Vilar D, Cabezas-Cerrato J. Non-insulin-mediated glucose uptake in several insulin-resistant states in the postabsorptive period. *Diabetes Res Clin Pract* 1998; **39**: 107–13

17 Rossi L, Thiene G, Caregaro L, Giordano R, Lauro S. Dysrhythmias and sudden death in acromegalic heart disease. *Chest* 1977; **72**: 495–8

18 Lie JT. Pathology of the heart in acromegaly: Anatomic findings in 27 autopsied patients. *Am Heart J* 1980; **100**: 41–52

19 McGuffin WL Jr, Sherman BK, Roth J, *et al.* Acromegaly and cardiovascular disorders: a prospective study. *Ann Intern Med* 1974; **81**: 11–18

20 Evans CC, Hipkin LJ, Murray GM. Pulmonary function in acromegaly. *Thorax* 1977; **32**: 322–7

21 Stern LZ, Payne CM, Hannapel LK. Acromegaly: histochemical and electron microscopic changes in deltoid and intercostal muscle. *Neurology* 1974; **24**: 589–93

22 Rosner B. *Fundamentals of Biostatistics*, 3rd Edn. Boston: PWS Kent, 1990

23 Norusis M. *SPSS for Windows Base System Users Guide Release 6.0.* Chicago: SPSS Inc., 1993

24 Sieber FE, Traystman RJ. Special Issues: Glucose and the Brain. *CCM* 1992; **20**: 104–14

British Journal of Anaesthesia 84 (2) 183–9 (2000)

BJA

LABORATORY INVESTIGATIONS

NOx– concentrations in the rat hippocampus and striatum have no direct relationship to anaesthesia induced by ketamine†

J. Wu, T. Kikuchi, Y. Wang, K. Sato and F. Okumura*

Department of Anaesthesiology, Yokohama City University School of Medicine, Yokohama 236-0004, Japan

**Corresponding author*

Using microdialysis, we have examined the effects of ketamine on concentrations of total nitric oxide oxidation products (NOx–) in the rat hippocampus and striatum *in vivo* to investigate the relationship between anaesthesia and NOx– production in the brain. Ketamine 25, 50 and 100 mg kg^{-1} i.p. increased NOx– concentrations to mean 125 (SD 13)%, 165 (11)% and 193 (13)% of basal, respectively, in the hippocampus and to 122 (12)%, 147 (7)% and 177 (14)% of basal in the striatum. Local perfusion with ketamine 50 and 100 μmol $litre^{-1}$ into the hippocampus or striatum increased NOx– concentrations to 212 (32)% and 291 (17)% of basal, respectively, in the hippocampus and to 148 (20)% and 201 (18)% of basal in the striatum. Ketamine 50 and 100 mg kg^{-1} i.p. caused dose-dependent prolongation of loss of the righting reflex (LRR) and 100 mg kg^{-1} i.p. also caused loss of the corneal reflex (LCR). Local perfusion of ketamine did not provoke LRR or LCR. Inhibition of NOS by L-NAME 100 mg kg^{-1} i.p. decreased hippocampal NOx– concentrations to 58 (7)% of basal and did not provoke LRR or LCR. Although the effect of ketamine-induced increases in hippocampal NOx– concentrations was significantly depressed by L-NAME, LRR was not affected. These data imply that NOx– concentrations in the hippocampus or striatum have no direct relationship to the anaesthetic efficacy of ketamine, although this requires further investigation.

Br J Anaesth 2000; **84**: 183–9

Keywords: measurement techniques, microdialysis; pharmacology, nitric oxide; anaesthetics i.v., ketamine, brain, hippocampus; brain, striatum; rat

Accepted for publication: September 2, 1999

Nitric oxide is a highly reactive and unstable free radical species and has been demonstrated to be a mediator of diverse physiological functions, including signal transmission, transduction and defence mechanisms in the central and peripheral nervous system.[1] Several studies have suggested a role for nitric oxide in mediating central nociceptive pathways and possible involvement in the mechanism of wakefulness and anaesthesia.[2 3]

Nitric oxide exerts many of its effects by increasing intracellular concentrations of cyclic guanosine monophosphate (cGMP) in target cells via activation of soluble guanylate cyclase.[4] Stimulation of excitatory amino acid (EAA) receptors increases nitric oxide production.[1] Suppression of excitatory transmission stimulated by excitatory amino acids or augmentation of inhibitory transmission via gamma-aminobutyric acid (GABA) receptors results in a sedating effect. Some anaesthetics may suppress excitatory transmission at any step in the glutamate receptor–nitric oxide–cGMP pathway. In fact, there is increasing evidence that blocking the glutamate receptor–nitric oxide–cGMP pathway may be associated with the development of anaesthesia. For example, 2-amino-6-(trifluoromethoxy)-benzothiazole (riluzole), both a pre- and postsynaptic inhibitor of glutamate, exerts an anaesthetic action.[5] Non-competitive antagonists at NMDA receptors, such as MK-801, SKF10047, phencyclidine and dextrorphan, can potentiate anaesthesia.[6 7]

Ketamine is also known as a non-competitive antagonist of NMDA receptors.[8] Because ketamine blocks excitation of NMDA receptors, it may influence nitric oxide production in the brain. Several reports have demonstrated that ketamine affects the glutamate receptor–nitric oxide–cGMP pathway *in vitro*.[9–11] However, this has not been confirmed in living animals by direct measurement of nitric oxide or nitric oxide oxidation products.

---

†This article is accompanied by Editorial II.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

In this study, using *in vivo* brain microdialysis coupled with online analysis of total nitric oxide oxidation products (NOx–), we have investigated the effects of ketamine, with or without S(+)-N^5-[imino(nitroamino)methyl]-L-ornithine methyl ester hydrochloride (L-NAME), an NOS inhibitor, on NOx– concentrations in the rat hippocampus and striatum to determine the relationship between NOx– concentration and anaesthesia induced by ketamine.

Materials and methods

The study was approved by the Animal Welfare Committee of Yokohama City University School of Medicine. The microdialysis technique in freely moving rats was used. Adult male Sprague–Dawley rats (7–8 weeks old, weighing 250–350 g) were anaesthetized with pentobarbital 50 mg kg^{-1} i.p. and then placed in a stereotaxic apparatus (Model SR-6, Narisige Scient Instrument LAB, Japan). A guide cannula (CMA 10, Carnegie Medicine, Sweden) for penetration of a microdialysis probe was stereotaxically implanted into the right hippocampus or right striatum according to the atlas of Paxinos and Watson,[12] as described previously.[13] The probe was fixed in place with cranioplastic cement. A stainless steel dummy probe was inserted into the guide cannula until a dialysis probe was inserted.

The rats were kept in a 12-h light–dark cycle in a regulated environment (23±2°C, 50% humidity, free access to water and food) for at least 48 h after the surgical procedure. At the beginning of the experiment, a microdialysis probe (3 mm long dialysis membrane, 0.24 mm od, molecular weight cut-off 20 000 Da; CMA11, Carnegie Medicine, Sweden) was inserted through the implanted guide cannula into the hippocampus or striatum. The probe was perfused with artificial cerebrospinal fluid (NaCl 147.0 mmol $litre^{-1}$, KCl 4.0 mmol $litre^{-1}$, $CaCl_2$ 3.0 mmol $litre^{-1}$, pH 7.4) at a constant flow rate of 2 μl min^{-1} with a microdialysis pump (Model CMA 102, Carnegie Medicine, Sweden).

The rats were kept in a plastic cage where they could move freely and had access to food and water during the dialysis experiment. After 2 h of dialysis equilibration, the dialysate was collected every 20 min in an automated sample injector connected to an automated nitric oxide detector–HPLC–spectrophotometer system (ENO-20, Eicom, Japan). Briefly, in this system, NO_2– and NO_3–, the stable oxidation products of nitric oxide in the dialysate, were separated using a reverse-phase separation column packed with polystyrene polymer (NO-PAK, 4.6×50 mm, Eicom, Japan). NO_3– was reduced to NO_2– in a reduction column packed with copper-plated cadmium filings (NO-RED, Eicom). NO_2– was mixed with a Griess reagent to form a purple azo dye in a reaction coil. The absorbance of the colour of the dye product at 540 nm was measured by a flow-through spectrophotometer. The quantity of NO_2– and NO_3– was calculated and recorded on a personal computer using specialized software (PowerChrom, ADInstruments Pty Ltd, Australia). NOx– was the sum of NO_2– and NO_3–. This assay system has been demonstrated as feasible for online assessment of nitric oxide production in living animals by measuring NOx–.[14 15]

At the end of the experiments, rats were killed by an overdose of diethyl ether and the correct position of the probe was verified by histological examination of the fibre tract.

Ketamine was purchased from Sankyo Co., Tokyo, Japan. L-NAME was purchased from Research Biochemicals International, Natick, MA, USA. All test agents were administered when three consecutive stable dialysis samples (basal level) had been collected after an equilibration period of 2 h of brain perfusion.

Anaesthesia was defined as loss of the righting reflex (LRR)[16] and loss of the corneal reflex (LCR).[17] LCR was defined as a deeper level of anaesthesia than LRR. These methods have been demonstrated to be related to the depth of anaesthesia in the rat.[18]

All data are expressed as mean (SD) values of NOx– in extracellular fluid (ECF) in the rat hippocampus or striatum. Statistical analysis was performed using StatView for Windows (Abacus Concepts, Inc., CA, USA). The Kruskal–Wallis test was used to analyse differences in NOx– concentrations between different experimental groups. If the overall difference in NOx– concentrations between different experimental groups was significant, differences in mean NOx– concentrations at individual times between control and each drug-treated group were analysed using the Mann–Whitney *U* test. Percentage change in NOx– was calculated by comparing NOx– concentrations after treatment with basal levels in each group, obtained by averaging NOx– concentrations in the three consecutive dialysate samples collected before treatment. Behavioural effects were analysed using the Mann–Whitney *U* test. Differences were considered significant at $P<0.05$.

Results

In vitro recovery of NO_2– and NO_3–was 30.9 (1.8)% and 35.1 (3.4)% (n=4), respectively, determined by perfusing the microdialysis probe directly in a mixture of $NaNO_2$ 10^{-6} mol $litre^{-1}$ and $NaNO_3$ 10^{-6} mol $litre^{-1}$ standard solution at 35°C, at a flow rate of 2 μl min^{-1}. Accordingly, basal NOx– in the dialysate was 0.15 (0.04)) μmol $litre^{-1}$ (n=58) and 0.21 (0.05) μmol $litre^{-1}$ (n=28) in the rat hippocampus and striatum, respectively. Therefore, given similar *in vivo* recovery, basal NOx– concentrations in ECF were 0.42 (0.12)) μmol $litre^{-1}$ and 0.59 (0.14)) μmol $litre^{-1}$ in the rat hippocampus and striatum, respectively.

Figure 1 shows the effects of ketamine on NOx– concentrations in the ECF of the hippocampus or striatum. Ketamine 25, 50 and 100 mg kg^{-1} i.p. induced increases in NOx– concentrations both in the hippocampus (Fig. 1A) and striatum (Fig. 1B) in a dose-dependent manner. Mean maximum NOx– concentrations after ketamine 25, 50 and

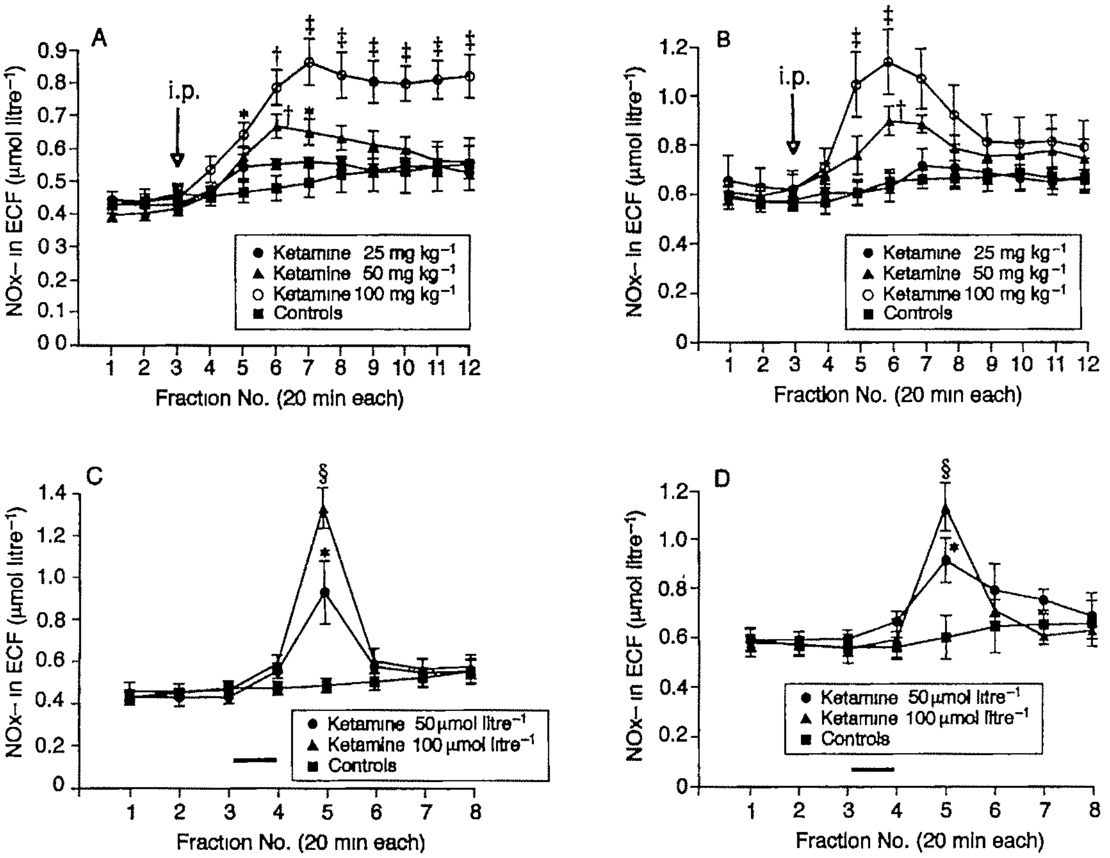


Fig 1 Effects of ketamine i.p. (A, B) or local perfusion (C, D) on NOx– concentrations in ECF in the rat hippocampus (A, C) or striatum (B, D) Ketamine was administered after three consecutive stable dialysis samples (basal) had been collected. A, B: Ketamine 25, 50 or 100 mg kg^{-1} was administered i p. C, D: Ketamine 50 or 100 µmol litre^{-1} was perfused locally into the hippocampus (C) or striatum (D). Data are mean (SD) NOx– concentrations of 4–7 different experiments. *$P<0.05$ *vs* respective control; †$P<0.05$ *vs* respective control and 25 mg kg^{-1}; ‡$P<0.05$ *vs* respective control, 25 mg kg^{-1} and 50 mg kg^{-1}; §$P<0.05$ *vs* respective control and 50 µmol litre^{-1} (Kruskal–Wallis test followed by the Mann–Whitney *U* test).

100 mg kg^{-1} i.p. were 0.57 (0.07) µmol litre^{-1} ($n=6$, $P>0.05$ *vs* control), 0.67 (0.07) µmol litre^{-1} ($n=6$, $P<0.05$ *vs* control) and 0.87 (0.11) µmol litre^{-1} ($n=7$, $P<0.05$ *vs* control) (125 (13)%, 165 (11)% and 193 (13)% of basal, respectively) in the hippocampus, and 0.71 (0.09) µmol litre^{-1} ($n=5$, $P>0.05$ *vs* control), 0.90 (0.06) µmol litre^{-1} ($n=5$, $P<0.05$ *vs* control) and 1.13 (0.16) µmol litre^{-1} ($n=5$, $P<0.05$ *vs* control) (122 (12)%, 147 (7)% and 177 (14)% of basal, respectively) in the striatum. Local perfusion of ketamine 50 and 100 µmol litre^{-1} into the hippocampus or striatum through the microdialysis probe provoked dose-dependent increases in NOx– concentrations in both the hippocampus (Fig. 1C) and striatum (Fig. 1D). Mean maximum NOx– concentrations were 0.91 (0.29) µmol litre^{-1} ($n=6$, $P<0.05$ *vs* control) and 1.31 (0.22) µmol litre^{-1} ($n=6$, $P<0.05$ *vs* control) (212 (32)% and 291 (17)% of basal, respectively) in the hippocampus, and 0.92 (0.18) µmol litre^{-1} ($n=4$, $P<0.05$ *vs* control) and 1.14 (0.21) µmol litre^{-1} ($n=4$, $P<0.05$ *vs* control) (148 (20)% and 201 (18)% of basal, respectively) in the striatum.

Ketamine 25 mg kg^{-1} i.p. did not provoke LRR or LCR. Ketamine 50 and 100 mg kg^{-1} i.p. provoked dose-dependent prolongation of LRR but only the 100 mg kg^{-1} dose resulted in LCR (Table 1). Local perfusion of ketamine 50 and 100 µmol litre^{-1} into the hippocampus or striatum via the microdialysis probes did not provoke LRR or LCR.

Table 1 Effects of ketamine with or without L-NAME, on loss of the righting reflex (LRR) (mean (SD)) and loss of the corneal reflex (LCR). L-NAME i p was administered alone or with ketamine 50 mg kg^{-1} i p, 60 min later *$P<0.05$ *vs* ketamine 50 mg kg^{-1} (Mann–Whitney *U* test)

Drugs	Duration of LRR (min)	LCR
Control ($n=7$)	Absent	Absent
Ketamine 25 mg kg^{-1} i p ($n=11$)	Absent	Absent
Ketamine 50 mg kg^{-1} i p. ($n=12$)	16.3 (11.1)	Absent
Ketamine 100 mg kg^{-1} i.p ($n=12$)	45.7 (19.4)*	Present
L-NAME 100 mg kg^{-1} i.p ($n=6$)	Absent	Absent
L-NAME 100 mg kg^{-1} i p.+ ketamine 50 mg kg^{-1} i.p. ($n=6$)	16.9 (10.5)	Absent

L-NAME 100 mg kg^{-1} i.p., an NOS inhibitor, caused a decrease in NOx– concentrations in the hippocampus. The mean minimum NOx– concentration was 0.24 (0.02) µmol litre^{-1} ($n=6$, $P<0.05$ *vs* control) (58 (7)% of basal) and NOx– concentrations remained decreased for 180 min. L-NAME 100 mg kg^{-1} i.p. did not provoke LRR or LCR. When NOx– concentrations were reduced by pretreatment

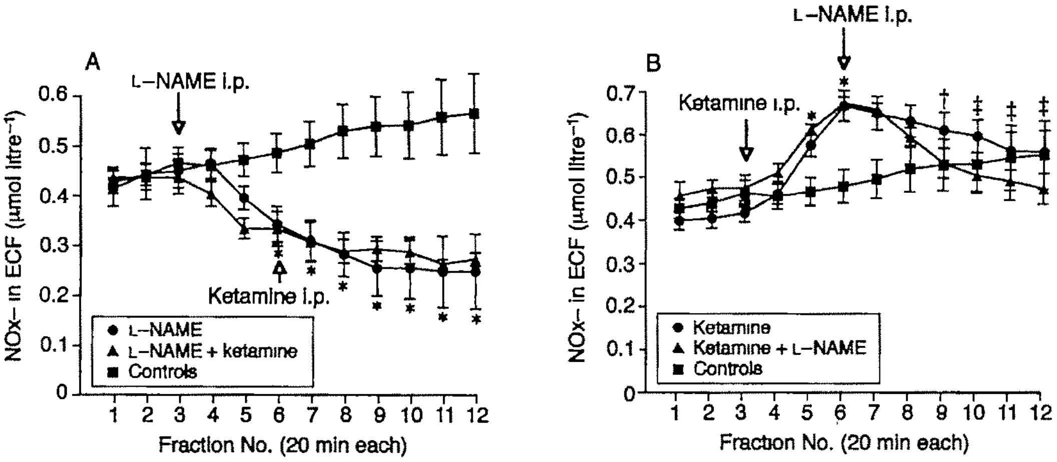


Fig 2 Effect of L-NAME on NOx− concentrations in ECF in the rat hippocampus A. After three consecutive stable dialysis samples (basal) had been collected, L-NAME 100 mg kg^{-1} i p was administered alone or with ketamine 50 mg kg^{-1} i p., 60 min later. B· After three consecutive stable dialysis samples (basal) had been collected, ketamine i.p. was administered alone or with L-NAME 100 mg kg^{-1} i.p. (K+L), 60 min later. Data are mean (SD) NOx− concentrations in 6–7 different experiments. *$P<0.05$ *vs* control, †$P<0.05$ *vs* control and K+L; ‡$P<0.05$ *vs* K+L (Kruskal–Wallis test followed by the Mann–Whitney *U* test).

with L-NAME 100 mg kg^{-1} i.p., subsequent administration of ketamine 50 mg kg^{-1} i.p. did not result in a stimulating effect on NOx− production (Fig. 2A) but ketamine induced LRR and its duration was not different from that induced by ketamine 50 mg kg^{-1} i.p. alone (Table 1). After NOx− concentrations in the hippocampus had been increased by ketamine 50 mg kg^{-1} i.p., subsequent administration of L-NAME 100 mg kg^{-1} i.p. significantly decreased the magnitude of the ketamine-induced increase in NOx− concentrations (Fig. 2B).

Discussion

We have demonstrated that ketamine increased NOx− concentrations in the hippocampus and striatum in both anaesthetized and non-anaesthetized rats *in vivo* and inhibition of the activity of NOS attenuated this effect of ketamine.

The mechanism of general anaesthesia remains largely unknown. Many theories consider that general anaesthesia is primarily the result of altered synaptic transmission. Depression of excitatory transmission and enhancement of inhibitory transmission are related to general anaesthesia.[19] As nitric oxide plays an important role in excitatory synaptic transmission, more and more attention has been paid to the effects of nitric oxide on anaesthesia. In the central nervous system (CNS), glutamate receptor–nitric oxide–cGMP pathways have been demonstrated in the cerebellum, hypothalamus, midbrain, striatum and hippocampus. Nitric oxide may be an important neurotransmitter in these regions.[20] Activation of NMDA receptors promotes an increase in intracellular calcium which causes activation of NOS, which then increases nitric oxide production.[1] The glutamate receptor–nitric oxide–cGMP pathway in the hippocampus is believed to play an important role in several physiological (i.e. learning and memory) and pathophysiological (i.e. epilepsy and neurodegenerative diseases) conditions.[21] The striatum is known as a very important region for control of motor activity. Therefore, the effect of anaesthetics on the glutamate receptor–nitric oxide–cGMP pathway in these regions is important.

Ketamine acts as an antagonist of NMDA-mediated transmission by blocking the phencyclidine site at the NMDA receptor complex.[8] Therefore, we expected that ketamine may decrease nitric oxide production by blocking NMDA receptors. In fact, some studies showed that ketamine inhibits nitric oxide production[9] and NOS activity *in vitro*[10 11] although there are no *in vivo* data to support this. As Ohta and colleagues demonstrated that NOx− concentrations in the dialysate were related to nitric oxide production *in vivo* using *in vivo* brain microdialysis,[14 15] in our study we measured NOx− concentrations in anaesthetized and freely moving rat brains. Our results showed that NOx− concentrations dose-dependently increased in rats anaesthetized with ketamine. To examine if these phenomena were related to the effect of ketamine-induced general anaesthesia, we also tested the effects of ketamine on NOx− concentrations in non-anaesthetized rats by local perfusion of ketamine 50 or 100 μmol litre^{-1} into the hippocampus or striatum. Although these concentrations are clinically relevant serum concentrations after anaesthesia with ketamine in animals,[22] local perfusion at these doses into the hippocampus or striatum did not provoke LRR or LCR. Also, under these conditions, ketamine caused dose-dependent increases in NOx− concentrations in the hippocampus and striatum. These results demonstrate that ketamine induced dose-dependent increases in NOx− concentrations in the rat hippocampus and striatum in both anaesthetized and non-anaesthetized animals.

Our results are different from previous *in vitro* studies using mouse-activated macrophage-like cells[9] or lipopolysaccharide-treated rat alveolar macrophages.[10] One of the reasons for the discrepancy is that the concentration of ketamine used in their studies was much higher than the serum concentration of ketamine used for anaesthetic doses. Reported serum concentrations of ketamine for anaesthesia in animals are less than 80 μmol litre^{-1}.[22] However, the concentration of ketamine used in the study of Shimaoka and colleagues[9] was up to 600 μmol litre^{-1}, which was much higher than that used for local perfusion into the brain in our study. Although Galley and Webster[11] demonstrated that ketamine decreased NOS activity at concentrations as low as 0.01 μmol litre^{-1}, they measured NOS activity *in vitro* using a method based on the quantitative conversion of oxyhaemoglobin to methaemoglobin while we quantitatively assayed NOx– by *in vivo* microdialysis. This may be a reason for the discrepancy. Another explanation is that they studied a different isoform of NOS (iNOS), expressed in endothelium, vascular smooth muscle and activated neutrophils and macrophages,[9 10] while most of the NOS isoforms in the brain are cNOS and nNOS. In an *in vitro* study in rat cerebellar slices, ketamine did not alter basal cGMP concentrations when no exogenous stimulant was given, but suppressed exogenous L-glutamate- and NMDA-stimulated cGMP formation.[23] This study implied that ketamine may not directly affect NOS or guanylate cyclase activities in the brain.

Differences in *in vivo* and *in vitro* experiments may also be an important reason for the discrepancy. In animals, the hippocampus and striatum receive neuronal inputs from other regions of the brain. Tonic inhibitory and phasic excitatory regulation of the activity of glutamate receptors has been demonstrated in the hippocampus and striatum *in vivo*.[24] The activity of the glutamate receptor–nitric oxide–cGMP pathway in the hippocampus and striatum may be affected by neuronal inputs from other regions of the brain In an *in vitro* preparation, these neuronal inputs are removed. Thus basal activity and release of most neuronal systems may be profoundly affected by removal of inputs from other regions of the brain.

The reason why ketamine, an NMDA receptor antagonist, increases NOx– concentrations in the rat hippocampus and striatum is not known. A possible mechanism may be that ketamine increases NOx– concentrations via an increase in acetylcholine (ACh) release in the brain. In our previous study,[13] ketamine produced a dose-dependent increase in ACh from the rat hippocampus and striatum *in vivo*. In the study of Giovanini and colleagues,[25] intracerebroventricular administration of the NMDAantagonists, 3-((RS)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), D(-)-2-amino-7-phosphonoheptanoic acid (D-AP7) or MK-801 increased ACh outflow from the rat hippocampus. ACh was the first neurotransmitter shown to indirectly affect the tone of blood vessels by causing release of a substance termed endothelium-dependent relaxing factor,[26] which has been demonstrated to be nitric oxide.[27] A recent study showed that ACh and nicotine may evoke nitric oxide release in the rat hippocampal slice.[28] Therefore, in our study, the effect of ketamine-evoked increases in NOx– concentrations in the hippocampus and striatum may have been caused partly by ketamine-induced increase in ACh in this region.

Another explanation is that ketamine may affect the outflow of endogenous EAA. In the study of Liu and Moghaddam, local application of an NMDA receptor antagonist, 2-amino-5-phosphonopentanoic acid (AP5), dose-dependently increased basal outflow of endogenous glutamate and aspartate in the hippocampus and striatum of freely moving rats, possibly because of a decrease in presynaptic ongoing inhibitory processes that control basal outflow of EAA.[24] Similarly, in our study, ketamine may have decreased these presynaptic ongoing inhibitory processes, resulting in an increase in the outflow of glutamate or aspartate, or both, which in turn activated other subtypes of glutamate receptors not blocked by ketamine. As stimulation of non-NMDA receptors and metabotropic glutamate (mGlu) receptors increased nitric oxide production in the rat hippocampus *in vivo*,[29 30] the increased endogenous glutamate and/or aspartate may activate non-NMDA receptors and/or mGlu receptors to increase NOx–. This remains to be elucidated.

Moreover, Smirnova, Stinnakre and Malled demonstrated the existence of an inhibitory presynaptic mechanism that controls the release of glutamate.[31] Local perfusion of the NMDA receptor antagonist, CPP, into the hippocampus resulted in a decrease in GABA outflow from the rat hippocampus.[25] Thus ketamine may decrease presynaptic GABA outflow, which in turn increases the release of endogenous glutamate and/or reduces inhibition of non-NMDA and mGlu receptors, resulting in an increase in NOx– release from the hippocampus and striatum.

As nitric oxide is synthesized by NOS, inhibition of NOS activity by an NOS inhibitor would be expected to decrease nitric oxide production. In our study, L-NAME, an NOS inhibitor, significantly decreased NOx– concentrations. This is in agreement with a previous study[15] and proves that NOx– concentrations in dialysate are related to nitric oxide production in the hippocampus and striatum *in vivo*. The fact that L-NAME significantly decreased the magnitude of ketamine-enhanced NOx– concentrations and pretreatment with L-NAME significantly depressed the stimulating effect of ketamine on NOx– production implies that by whichever mechanism, inhibition of NOS activity attenuates the stimulating effect of ketamine on NOx– production *in vivo*.

The effect of nitric oxide on anaesthesia is still controversial. Johns, Moscicki and DiFazio showed that inhibition of NOS activity reduced the minimum alveolar anaesthetic concentration of halothane in the rat.[2] But Adachi and colleagues reported an opposite effect.[32] Also, it is not proved that inhibition of NOS activity reduces the anaesthetic requirements for i.v. anaesthetics.[33 34] In our study, ketamine produced a dose-dependent increase in NOx– concentrations in the hippocampus. If NOx– concentration in the hippocampus are related to the anaesthetic efficacy of ketamine, decreased NOx– concentrations in the hippocampus by pretreatment of rats with L-NAME should decrease the duration of LRR induced by ketamine. However, our results did not support this speculation. The duration of LRR provoked by ketamine 50 mg kg^{-1} i.p. was not decreased by pretreatment with L-NAME 100 mg kg^{-1} i.p. This dose of L-NAME has been demonstrated to be sufficient to inhibit more than 90% of NOS activity in the rat hippocampus *in vivo*[35] and decreased NOx– concentrations to 58% of basal in our study. Although these data did not allow us to draw firm conclusions on the relationship between NOx– concentrations in the hippocampus and the anaesthetic efficacy of ketamine, our data imply that NOx– concentrations in the hippocampus are not related to the anaesthetic efficacy of ketamine.

In summary, ketamine produced an increase in NOx– concentrations in the hippocampus and striatum in both anaesthetized and non-anaesthetized rats *in vivo*. Inhibition of NOS activity by L-NAME attenuated this effect of ketamine without diminishing the anaesthetic effects of ketamine. These results imply that NOx– concentrations in the hippocampus or striatum are not related directly to the anaesthetic efficacy of ketamine, although further investigation is required.

References

1 Garthwaite J. Glutamate. Nitric oxide and cell–cell signalling in the nervous system. *Trends Neurosci* 1991; **14**: 60–7

2 Johns RA, Moscicki JC, DiFazio CA. Nitric oxide synthase inhibitor dose-dependently and reversibly reduces the threshold for halothane anaesthesia: a role for nitric oxide in mediating consciousness? *Anesthesiology* 1992; **77**: 779–84

3 Nakamura K, Mori K. Nitric oxide and anesthesia. *Anesth Analg* 1993; **77**: 877–9

4 Luo D, Leung E, Vincent SR. Nitric oxide-dependent efflux of cGMP in rat cerebellar cortex: an in vivo microdialysis study. *J Neurosci* 1994; **14**: 263–71

5 Mantz J, Cheramy A, Thierry AM, Glowinski J, Desmonts JM. Anesthetic properties of riluzole (54274 RP), a new inhibitor of glutamate neurotransmission. *Anesthesiology* 1992; **76**: 844–8

6 France CP, Snyder AM, Woods JH. Analgesic effects of phencyclidine-like drugs in rhesus monkeys. *J Pharmacol Exp Ther* 1989, **250**: 197–201

7 Daniell LC. The noncompetitive N-methyl-D-aspartate antagonists, MK-801, phencyclidine and ketamine increase the potency of general anesthetics. *Pharmacol Biochem Behav* 1990; **36**: 111–15

8 Thomson AM, West DC, Lodge D. An N-methylaspartate receptor-mediated synapse in rat cerebral cortex: a site of action of ketamine? *Nature* 1985; **313**: 479–81

9 Shimaoka M, Iida T, Ohara A, *et al.* Ketamine inhibits nitric oxide production in mouse-activated macrophage-like cells. *Br J Anaesth* 1996; **77**: 238–42

10 Li CY, Chou TC, Wong CS, *et al.* Ketamine inhibits nitric oxide synthase in lipopolysaccharide-treated rat alveolar macrophages. *Can J Anaesth* 1997; **44**: 989–95

11 Galley HF, Webster NR. Brain nitric oxide synthase activity is decreased by intravenous anesthetics. *Anesth Analg* 1996; **83**: 591–4

12 Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coodinates*, 2nd Edn. New York. Academic Press, 1986

13 Sato K, Wu J, Kikuchi T, Wang Y, Watanabe I, Okumura F. Differential effects of ketamine and pentobarbitone on acetylcholine release from the rat hippocampus and striatum. *Br J Anaesth* 1996; **77**: 381–4

14 Ohta K, Araki N, Shibata M, *et al.* A novel assay system for consecutive measurement of brain nitric oxide production combined with the microdialysis technique. *Neurosci Lett* 1994; **176**: 165–8

15 Yamada K, Nabeshima T. Simultaneous measurement of nitrite and nitrate levels as indices of nitric oxide release in the cerebellum of conscious rats. *J Neurochem* 1997; **68**: 1234–43

16 Danhof M, Levy G. Kinetics of drug action in disease states. I. Effect of infusion rate on phenobarbital concentrations in serum, brain and cerebrospinal fluid of normal rats at onset of loss of righting reflex. *J Pharmacol Exp Ther* 1984; **229**: 1–7

17 Tervo T, Jo F, Huikuri KT, Toth I, Palkama A. Fine structure of sensory nerves in the rat cornea: an experimental nerve degeneration study. *Pain* 1979; **6**: 57–70

18 Gustafsson LL, Ebling WF, Osaki W, Stanski DR. Quantitation of depth of thiopental anesthesia in the rat. *Anesthesiology* 1996; **84**: 415–27

19 Keane PE, Biziere K. The effects of general anesthetics on GABAergic synaptic transmission. *Life Sci* 1987; **41**:1437–48

20 Forstermann U, Gorsky LD, Pollock JS, Schmidt HH, Heller M, Murad F. Regional distribution of nitric oxide synthesizing enzyme(s) in rat brain. *Biochem Biophysiol Res Commun* 1990; **168**: 727–32

21 Bennett MK, Drejer J, Schousboe A, Diemer NH. Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. *J Neurochem* 1984; **43**: 1369–74

22 Schwieger IM, Szlam F, Hug CC Jr. The pharmacokinetics of ketamine in dogs anesthetized with enflurane. *J Pharmacokinet Biopharmacol* 1991; **19**: 145–56

23 Miyawaki I, Nakamura K, Yokubol B, Kitamura R, Mori K. Suppression of cyclic guanosine monophosphate formation in rat cerebellar slices by propofol, ketamine and midazolam. *Can J Anaesth* 1997: **44**: 1301–7

24 Liu J, Moghaddam B. Regulation of glutamate efflux by excitatory amino acid receptors: evidence for tonic inhibitory and phasic excitatory regulation. *J Pharmacol Exp Ther* 1995; **274**: 1209–15

25 Giovannini MG, Mutolo D, Bianchi L, Michelassi A, Pepeu G. NMDA receptor antagonists decrease GABA outflow from the septum and increase acetylcholine outflow from the hippocampus: a microdialysis study. *J Neurosci* 1994; **14**:1358–65

26 Furchgott RF, Zawadski JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373–6

27 Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987; **327**: 524–6

28 Smith DA, Hoffman AF, David DJ, Adams CE, Gerhardt GA. Nicotine-evoked nitric oxide release in the rat hippocampal slice. *Neurosci Lett* 1998; **255**: 127–30

29 Bhardwaj A, Northington FJ, Ichord RI, Hanley DF, Traystman RJ, Koehler RC. Characterization of ionotropic glutamate receptor-mediated nitric oxide production in vivo in rats. *Stroke* 1997; **28**: 851–7

30 Bhardwaj A, Northington FJ, Martin LJ, Hanley DF, Traystman RJ, Koehler RC. Characterization of metabotropic glutamate receptor-mediated nitric oxide production in vivo. *J Cereb Blood Flow Metab* 1997; **17**: 153–60

31 Smirnova T, Stinnakre J, Mallet J. Characterization of a presynaptic glutamate receptor. *Science* 1993; **262**: 430–3

32 Adachi T, Kurata J, Nakao S, *et al.* Nitric oxide synthase inhibitor does not reduce minimum alveolar anesthetic concentration of halothane in rats *Anesth Analg* 1994, **78**: 1154–7

33 Tonner PH, Scholz J, Lamberz L, Schlamp N, Esch JS. Inhibition of nitric oxide synthase decreases anesthetic requirement of intravenous anesthetics in xenopus laevis *Anesthesiology* 1997; **87**:1479–85

34 Tobin JR, Martin LF, Breslow MJ, Traystman RJ. Selective anesthetic inhibition of brain nitric oxide synthase. *Anesthesiology* 1994; **81**: 1264–9

35 Bannerman DM, Chapman PF, Kelly PAT, Butcher SP, Morris RGM. Inhibition of nitric oxide synthase does not prevent the induction of long-term potentiation in vivo *J Neurosci* 1994, **14**: 7415–25

British Journal of Anaesthesia **84** (2). 190–6 (2000)

The neuronal nitric oxide synthase inhibitor 7-nitroindazole (7-NI) and morphine act independently on the control of breathing†

L. Teppema*, E. Sarton, A. Dahan and C. N. Olievier

Departments of Physiology and Anaesthesiology, Leiden University Medical Centre, Leiden, The Netherlands

**Corresponding author: Department of Physiology, Leiden University Medical Centre, PO Box 9604, 2300 RC Leiden, The Netherlands*

Inhibitors of nitric oxide synthase (NOS) have analgesic properties and reduce opioid tolerance and dependency. To investigate a possible interaction of NOS inhibitors with the respiratory depressant action of morphine, we determined the effects of the neuronal NOS inhibitor 7-nitroindazole (7-NI) on the ventilatory carbon dioxide response curve; subsequently, we studied the effects of additional morphine application. Finally, using naloxone, we investigated a possible interaction (at the opioid receptor) between the effects of 7-NI and morphine. The effects of 7-NI 50 mg kg^{-1} i.p., morphine 0.1 mg kg^{-1} i.v. and naloxone 0.1 mg kg^{-1} i.v. were studied using dynamic end-tidal carbon dioxide forcing in eight cats under α-choralose–urethane anaesthesia. Data analysis was performed using a two-compartment model comprising a fast peripheral and a slow central component characterized by carbon dioxide sensitivities and a single offset B (apnoeic threshold). 7-NI decreased the mean apnoeic threshold from 4.27 (SD 0.87) to 2.59 (1.71) kPa. Peripheral and central carbon dioxide sensitivities were reduced from 0.56 (0.22) to 0.26 (0.09) litre min^{-1} kPa^{-1} and from 0.09 (0.05) to 0.04 (0.03) litre min^{-1} kPa^{-1}, respectively. Morphine increased the apnoeic threshold by 0.5 kPa and reduced carbon dioxide sensitivity by a further 35%. Naloxone reversed the ventilatory effects of morphine but not those induced by 7-NI. We conclude that the respiratory effects of 7-NI and morphine are mediated independently and that the effects of 7-NI do not result from interaction with opioid receptors.

Br J Anaesth 2000; **84**: 190–6

Keywords: pharmacology, nitric oxide; analgesics opioid, morphine; ventilation, carbon dioxide response; receptors, opioid; receptors, chemoreceptors

Accepted for publication: September 20, 1999

Several studies have suggested a modulatory role for nitric oxide in the control of nociception, arousal and anaesthesia. Examples of these functions are the findings that: (1) inhibitors of the nitric oxide synthesizing enzyme, nitric oxide synthase (NOS), exhibit antinociceptive activity[1–3] and potentiate morphine-induced analgesia[4]; (2) NOS inhibitors reduce opioid tolerance and attenuate opioid withdrawal[5–7]; (3) the nitric oxide precursor L-arginine reduces the antinociceptive action of morphine[8 9] which can be reversed by NOS inhibition[8]; and (4) NOS inhibitors lower the threshold (MAC) for halothane and isoflurane anaesthesia.[10 11]

As there appears to be an interaction of NOS inhibitors and opioids for analgesia, the question arises if this may also apply to the well-known respiratory depressant actions of opioids. Pelligrino, Laurito and VadeBoncouer[12] showed that intracerebroventricularly applied nitro-L-arginine (LNA) to normocapnic awake dogs increased ventilation and reduced morphine-induced ventilatory depression. In the anaesthetized cat, LNA reduced ventilatory carbon dioxide sensitivity but decreased the apnoeic threshold (*X*-intercept of the ventilatory carbon dioxide response curve).[13] However, as LNA is a non-selective inhibitor of NOS, we were unable to determine if these effects were caused by inhibition of endothelial or neuronal NOS, or both.

In this study in anaesthetized cats, we have examined the effect of the selective neuronal NOS inhibitor 7-nitroindazole (7-NI) on the control of breathing and the effect of subsequent administration of morphine. To study

---

†This article is accompanied by Editorial II.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

the possible involvement of opioid receptors in the effect of both drugs, we also performed an additional naloxone administration. To measure the effects of these agents on the ventilatory carbon dioxide response curve, we applied dynamic end-tidal carbon dioxide forcing and analysed the data using a two-compartment model comprising a fast peripheral and a slow central component characterized by carbon dioxide sensitivities and a single offset (apnoeic threshold), respectively.[14 15]

Materials and methods

The experiments were performed after obtaining approval from the Ethics Committee for Animal Experiments of Leiden University Medical Centre. Eight cats of both sexes (body weight 2.6–5.0 kg) were sedated with ketamine 10 mg kg^{-1}. The animals were anaesthetized with gas containing 0.7–1.4% sevoflurane and 30% oxygen in nitrogen. The right femoral vein and artery were cannulated, and α-chloralose 20 mg kg^{-1} and urethane 100 mg kg^{-1} were given slowly i.v. and the volatile anaesthetic was withdrawn. Approximately 1 h later, an infusion of an α-chloralose–urethane solution was started at a rate of 1.0–1.5 mg kg^{-1} h^{-1} for α-chloralose and 5.0–7.5 mg kg^{-1} h^{-1} for urethane. This regimen produces a level of anaesthesia sufficient to suppress pain withdrawal reflexes but light enough to preserve the corneal reflex. The stability of the ventilatory variables was studied on a previous occasion,[13] and were found to be similar to those in awake animals, as indicated by the fact that they were stable over a period of at least 6 h.

To measure inspiratory and expiratory flow, the trachea was cannulated and connected via a Fleisch No. 0 transducer (Fleisch, Lausanne, Switzerland), which was connected to a differential pressure transducer (Statham PM197, LA, USA). With the aid of three computer steered mass flow controllers (Hi-Tec, Veenendaal, The Netherlands) the composition of the inspirate (pure oxygen, carbon dioxide and nitrogen) could be controlled. The inspiratory and expiratory fractions of oxygen and carbon dioxide were measured with a fast responding zirconium oxide cell (Jaeger, O_2-test, Würzburg, Germany) and an infrared analyser (Gould Godard MK-2 capnograph, Bilthoven, The Netherlands). Temperature was controlled within 1°C in each cat and ranged between 36.5 and 38.5°C. Femoral arterial pressure was measured with a strain gauge transducer (Statham P23aC, LA, USA). All signals were recorded on polygraphs and processed by a PDP 11/23 minicomputer (sample frequency 100 Hz). Tidal volume, breathing frequency, duration of inspiration and expiration, and end-tidal P_{CO_2} (PE'_{CO_2}) and P_{O_2} (PE'_{O_2}) were stored on a breath-by-breath basis.

Experimental design

In each cat, the carbon dioxide ventilatory response curve was determined by performing 2–4 dynamic end-tidal forcing (DEF) runs under four different conditions: (I) control; (II) 45–60 min after administration of 7-nitroindazole 50 mg kg^{-1} i.p. (7-NI, purchased from Sigma, Zwijndrecht, The Netherlands), dissolved in peanut oil 10 ml; (III) 20 min after a subsequent i.v. infusion of morphine 0.1 mg kg^{-1} (dissolved in NaCl); (IV) 20 min after administration of naloxone 0.1 mg kg^{-1} i.v. (dissolved in NaCl). Before 7-NI treatment, four animals were treated with 10 ml of vehicle (peanut oil) alone, and three DEF runs were performed.

The ventilatory response to carbon dioxide was studied using the DEF. As this method has been described previously,[15] only a brief description is given. We applied the DEF technique by imposing stepwise changes in end-tidal carbon dioxide tensions at a constant normoxic background PE'_{O_2} of approximately 15 kPa. Each DEF run started with a steady state period of about 2 min in which end-tidal P_{CO_2} was maintained at approximately 0.6 kPa above the resting value. Thereafter, PE'_{CO_2} was increased by 1–1.5 kPa within one or two breaths, maintained at a constant level for approximately 7 min and then reduced to the previous value and kept constant for another 7 min.

Data analysis

The steady state relationship of ventilation (V_I) to PE'_{CO_2} at a constant PE'_{O_2} is linear down to the PE'_{CO_2} axis and is well described by DeGoede and colleagues[15 16]:

$$\dot{V}_I=(G_p+G_c)\ (PE'_{CO_2}-B) \qquad (1)$$

where G_p=carbon dioxide sensitivity of the peripheral chemoreflex loop, G_c= carbon dioxide sensitivity of the central chemoreflex loop and B=apnoeic threshold or extrapolated PE'_{CO_2} at zero $\dot{V}_I$. The sum of G_p and G_c is the total carbon dioxide sensitivity (G_{tot}).

For analysis of the dynamic response of ventilation to a stepwise change in PE'_{CO_2}, we used a two-compartment model:

$$\dot{V}_p\ (t)+\tau_p\ d/dt\ \dot{V}_p\ (t)=G_p\ (PE'_{CO_2}\ [t-T_p]-B) \qquad (2)$$

$$\dot{V}_c\ (t)+\tau_c\ d/dt\ \dot{V}_c\ (t)=G_c\ (PE'_{CO_2}\ [t-T_c]-B) \qquad (3)$$

where τ_p and τ_c= time constants of the peripheral and central chemoreflex loops, respectively, $\dot{V}_p$ (t) and V_C (t)= outputs of the peripheral and central chemoreflex loops, respectively, PE'_{CO_2} $[t-T_p]$=stimulus to the peripheral chemoreflex loop delayed by the peripheral transport delay time (T_p), and PE'_{CO_2} $[t-T_c]$=stimulus to the central chemoreflex loop delayed by the central transport delay time (T_c).

To model τ_c of the ventilatory on-transient (i.e. the central time constant of the ventilatory response to a step increase in $PE'_{CO_2}=\tau_{on}$) to be different from the ventilatory off-transient (i.e. the central time constant of the ventilatory response to a step decrease in $PE'_{CO_2}=\tau_{off}$), τ_c is written as:

$$\tau_c = x\times\tau_{on}+(1-x)\ \tau_{off} \qquad (4)$$

where $x=1$ when PE'_{CO_2} is high and $x=0$ when PE'_{CO_2} is low.

In most experiments, a small drift in ventilation was

Table 1 Respiratory variables obtained in seven cats from the optimal model fits for controls, after 7-nitroindazole (7-NI) infusion, after subsequent morphine administration and after a final naloxone treatment. Values are mean (SD). G_p=Peripheral carbon dioxide sensitivity, G_c=central carbon dioxide sensitivity; G_{tot}=G_p+G_c, B=apnoeic threshold. **Morphine *vs* 7- NI, $P<0.01$; †††7-NI *vs* control, $P<0.0001$, ‡naloxone *vs* 7-NI, $P=0.0104$

	Control	7-NI	Morphine	Naloxone
No. of runs	33	25	22	18
G_c (litre min^{-1} kPa^{-1})	0.56 (0.22)	0.26 (0.09)†††	0.17 (0.07)**	0.23 (0.10)
G_p (litre min^{-1} kPa^{-1})	0.09 (0.05)	0.04 (0.03)†††	0.02 (0.02)	0.05 (0.02)
G_{tot} (litre min^{-1} kPa^{-1})	0.65 (0.25)	0.30 (0.12)†††	0.20 (0.08)**	0.28 (0.10)‡
B (kPa)	4.27 (0.87)	2.59 (1.71)†††	3.05 (1.56)**	2.63 (1.39)
Arterial pressure (kPa)	18.0 (1.5)	16.6 (1.2)†††	14.7 (2.3)**	17.2 (1.3)

present. Therefore, we included a drift term ($C\times t$) in our model. The total ventilatory response ($\dot{V}_I(t)$) is made up of the contributions of the central and peripheral chemoreflex loops, $C\times t$ and a measurement white noise term (W(t)):

$$\dot{V}_I(t) = \dot{V}_p(t) + V_c(t) + C\times t + W(t) \qquad (5)$$

The variables of the model were estimated by fitting the model to the breath-to-breath data using a least-squares method. To obtain optimal time delays, a 'grid search' was applied, and all combinations of T_p and T_c, with increments of 1 s and with $T_p \leq T_c$, were tried until a minimum in the residual sum of squares was obtained. The minimum time delay was chosen arbitrarily to be 1 s; τ_p was at least 0.3 s.

Statistical analysis

Results are presented as mean (SD). Differences between the four treatments (i.e. control [I], 7-NI [II], morphine [III] and naloxone [IV]) were analysed by analysis of variance (ANOVA) using a fixed model. The design of the analysis was directed to perform planned comparisons only (i.e. treatment II *vs* I, treatment III *vs* II and treatment IV *vs* II, respectively). Therefore, the level of significance was set at P=0.016.

Results

In the four animals tested, infusion of the vehicle did not result in measurable circulatory or respiratory changes, and the values of the estimated respiratory variables obtained by fitting the data were not different from those obtained before administration of the vehicle. One animal did not receive the final naloxone infusion and was therefore excluded from the ANOVA procedure. In Table 1, the results in the remaining seven animals, in which 98 DEF runs were performed (not including vehicles), are summarized. An example of DEF runs in one animal during each of the four experimental conditions is shown in Figure 1.

The mean values in Table 1 and Figure 2 show that 7-NI caused a considerable (approximately 50%) decrease in central (G_c) and peripheral (G_p) carbon dioxide sensitivities: from 0.56 (0.22) to 0.26 (0.09) litre min^{-1} kPa^{-1} and from 0.09 (0.05) to 0.04 (0.03) litre min^{-1} kPa^{-1}, respectively. Parameter B was reduced from 4.27 (0.87) to 2.59 (1.71) kPa. Subsequent infusion of morphine caused further reductions in G_c and G_p to 0.17 (0.07) and to 0.02 (0.02) litre min^{-1} kPa^{-1}, respectively, while parameter B increased to 3.05 (1.56) kPa. Similar effects of 7-NI and morphine were obtained in the animal not receiving the final naloxone treatment. Naloxone infusion, performed approximately 1 h after administration of morphine, reversed completely the effects of morphine: Figure 2 and the data in Table 1 show that the slope and X-intercept of the carbon dioxide response curve after naloxone were similar to those before infusion of morphine, but after 7-NI treatment.

An example of the acute effects of morphine and naloxone (both drugs were infused at the same constant $P\text{E}'_{CO_2}$) is shown in Figure 3. The main effect of morphine on $\dot{V}_I$ consisted of a decrease in tidal volume and a slight decrease in frequency. Infusion of naloxone restored ventilation to the level before infusion of morphine (in the example in Fig. 3, performed 65 min earlier).

Circulatory changes were modest: a mean decrease in arterial pressure of 10 mm Hg after 7-NI administration, a further decrease of 15 mm Hg after morphine and an increase of 19 mm Hg after naloxone, restoring pressure to pre-morphine values.

Discussion

The major findings in our study were that: (1) 7-NI decreased both the apnoeic threshold B and ventilatory carbon dioxide sensitivities of both the peripheral (G_p) and central (G_c) chemoreflex loops; (2) after prior administration of 7-NI, morphine produced a further reduction in G_p and G_c and an increase in B; and (3) naloxone completely reversed the ventilatory effects of morphine.

As we performed DEF runs under four different experimental conditions (baseline, 7-NI, morphine after 7-NI, 7-NI+morphine+naloxone), the total duration of the experiments was often several hours. Recently, we tested the stability of our anaesthetic regimen by performing several DEF runs during a time span of approximately 5 h.[13] The values of G_p, G_c and B showed no systematic changes over this period, and variabilities were comparable with those obtained in awake animals. Furthermore, it has been shown that our two-compartment model gives reliable estimates of G_p, G_c and B.[15]

Effects of 7-nitroindazole

The effects of the neuronal NOS inhibitor 7-NI on G_p and G_c were similar, as observed previously after administration of the non-selective inhibitor N$^{\omega}$-nitro-L-arginine (LNA),[13]

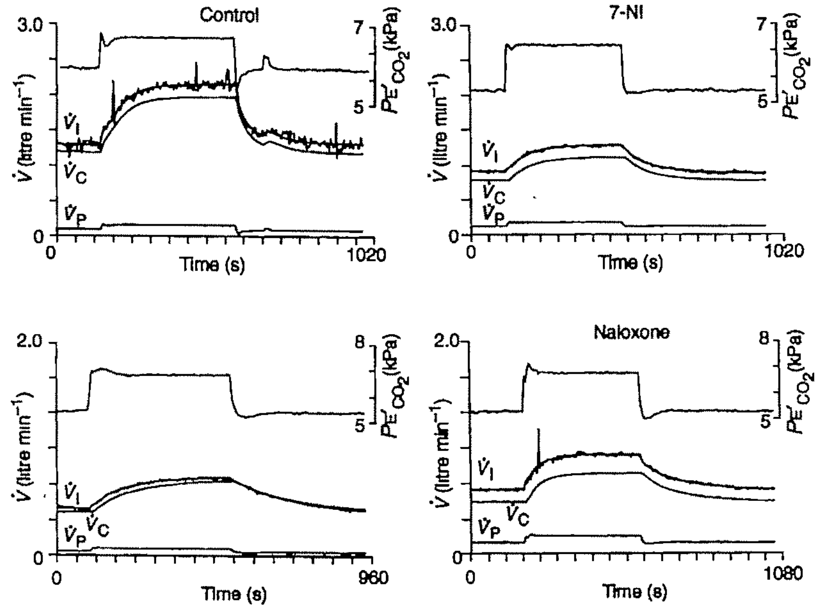


Fig 1 Examples of dynamic end-tidal forcing runs in each of the four experimental conditions in one animal. $\dot{V}$=Minute ventilation, $\dot{V}_c$=model output of central chemoreflex loop and $\dot{V}_p$=model output of peripheral chemoreflex loop. The noisy signal (best visible in the control panel) is the measured breath-by-breath ventilation The continuous line through these points is the modelled ventilatory output $\dot{V}_I$.

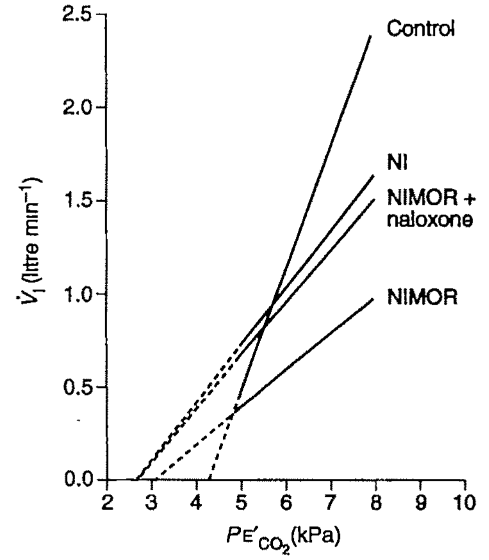


Fig 2 Steady state ventilatory carbon dioxide response curves under the following conditions controls, after 7-nitroindazole (NI), after morphine following 7-NI (NIMOR); and after naloxone following 7-NI+morphine (NIMOR+naloxone). Response curves are extrapolated down to the P_{CO_2} axis.

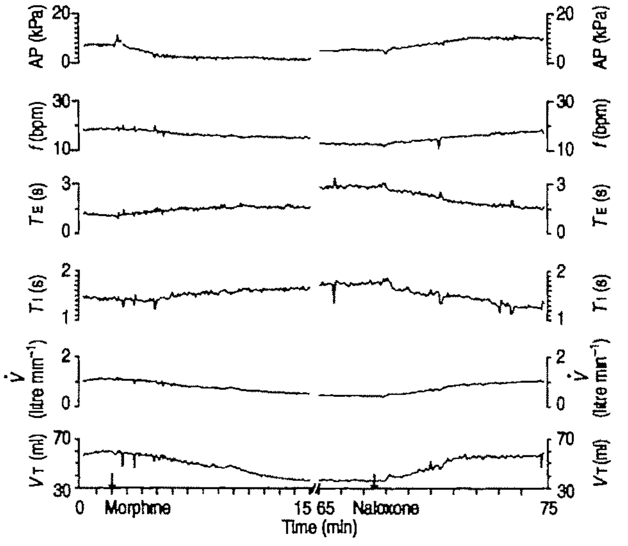


Fig 3 Effects of morphine and naloxone on arterial pressure (AP) and ventilation in a representative cat pretreated with the neuronal NOS inhibitor 7-nitroindazole. Inhibition of neuronal NOS did not prevent naloxone returning ventilatory measurements to pre-morphine values f= Respiratory frequency; T_E and T_I=expiratory and inspiratory durations, respectively, $\dot{V}$=minute ventilation; and V_T=tidal volume.

while the decrease in the apnoeic threshold (1.7 *vs* 1.1 kPa) was somewhat larger. The decrease in B could be a result of an increase in brain tissue P_{CO_2} secondary to a decrease in cerebral blood flow. Non-selective inhibitors of NOS cause a decrease in cerebral blood flow, particularly in pontomedullary tissue.[17 18] The reported effects of *neuronal* NOS inhibition on baseline cerebral arteriolar diameter or blood flow vary from only small reductions[19 20] to relatively large decreases.[21 22]

Apart from a decrease in cerebral blood flow, 7-NI may have caused a decrease in B by preventing the modulating influence of nitric oxide on the release of several neurotransmitters or on neurotransmitter-mediated processes (see references below). In the central nervous system, the action of nitric oxide is predominantly excitatory in nature.[23 24] Many data indicate that the *N*-methyl-D-aspartate (NMDA) glutamate receptor is the principle activator of NOS in the brain, responsible for release of nitric oxide on stimulation.[23 25 26] In cats and rats, the integrity and activation of glutamate receptors in NOS-containing respiratory regions of the nucleus tractus solitarius (NTS) and rostroventrolateral medulla are necessary for maintenance of normal levels of ventilation and for a normal ventilatory response to carbon dioxide (see Teppema and colleagues[27]). Among other factors, G_p depends on cerebrovascular and chemoreceptor sensitivities to changes in local P_{CO_2}. A reduction in cerebral blood flow response to changes in arterial P_{CO_2} should result in an *increase* in G_c. As 7-NI reduces cerebrovascular carbon dioxide sensitivity,[20] the observed *decrease* in G_c must result from powerful inhibition of the central pathways responsible for the hypercapnic response, involving nitric oxide-containing neurones known to be present in respiratory regions of the brain stem.[28–30]

Within the carotid bodies, nitric oxide acts as an inhibitory neuromodulator.[31 32] However, inhibition of NOS has been shown to reduce the hypoxic ventilatory response in cats and rats.[32 33] Hypoxia causes release of glutamate in NOS-containing NTS regions where chemoafferents from the carotid sinus nerve (CSN) terminate.[34 35] Furthermore, NOS inhibitors applied locally into the NTS significantly attenuate the hypoxic ventilatory response.[34] Therefore, the effect of NOS inhibition on the hypoxic response may reside in the NTS. If hypoxia-induced release of glutamate in the NTS is caused by increased afferent nerve activity rather than hypoxia per se, the hypercapnia-induced increase in CSN activity may also result in release of glutamate. Inhibition of neuronal NOS would thus result in a decrease in carbon dioxide sensitivity of the peripheral chemoreflex loop, explaining the observed decrease in G_p in this study. Gozal and colleagues reported that carotid body NOS is of mainly endothelial origin, explaining their observation that the non-selective inhibitor N-nitro-L-arginine methyl ester but not the neuronal inhibitor S-methyl-L-thiocitrulline enhanced the ventilatory response to NaCN.[32] It is possible therefore that the decrease in G_p by the neuronal inhibitor 7-NI that we found was caused entirely by inhibition of NOS within the NTS.

As reviewed by Pelligrino, Laurito and VadeBoncouer,[12] nitric oxide can also influence the release of several neurotransmitters, other than glutamate, which can modify ventilatory output. Examples are GABA and norepinephrine. Further studies using agents acting selectively on glutamate, GABA, α-adrenergic and glutamate receptors are necessary to investigate by which mechanisms NOS inhibitors can influence the neural control of breathing.

Using the neuronal inhibitor 7-NI, we studied the ventilatory response independent of vasoconstrictor effects resulting from inhibition of endothelial NOS (see also Moore and colleagues[2]). In contrast with our previous study in which we used the non-selective inhibitor LNA,[13] we did not observe an increase in arterial pressure but rather a small but significant decrease. The ventilatory effects induced by 7-NI, however, were similar to those observed after LNA. These results indicate that ventilatory effects caused by non-selective NOS inhibitors are caused predominantly by inhibition of neuronal NOS. Furthermore, the considerable increase in arterial pressure observed after LNA[13] does not seem to have an important neurogenic component and has a minor influence on the ventilatory effect induced by this non-selective NOS inhibitor. The modest decrease in arterial pressure after 7-NI may be a result of decreased effectiveness of the (glutamate-dependent) baro-afferent impulse transmission within the NTS, combined with inhibition of NOS in autonomic neurones in the rostroventrolateral medulla.[29] A decrease in arterial pressure may have a stimulatory effect on ventilation via the baroreflex pathway. To some extent this could have counteracted the inhibitory effects induced by 7-NI. However, as discussed previously,[13] changes in arterial pressure do not alter the slope of the carbon dioxide response curve. In addition, 7-NI may also have affected the efficiency of the glutamate-dependent baro-afferent impulse transmission within the NTS.

In the awake and anaesthetized rat, inhibition of neuronal NOS was reported not to change resting ventilation.[36 37] In the normocapnic awake dog, intracerebroventricular administration of LNA resulted in an increase in resting $\dot{V}_I$.[12] In none of these studies, however, was a decrease in ventilatory carbon dioxide sensitivity reported. Our results cannot be compared easily with these other studies because of variations in methodology and arousal state of the animals, and because of possible species differences. Gozal and colleagues[36] and Patel and colleagues[37] used $P_{E'CO_2}$ as the independent variable. However, in the former study, inspiratory changes from room air to air containing 5% carbon dioxide did not result in identical arterial P_{CO_2} changes before and after drug administration. Patel and colleagues[37] reported relatively large arterial-to end-tidal P_{CO_2} gradients, particularly in the hypercapnic range. Pelligrino, Laurito and VadeBoncouer[12] used ventilatory drive as an index, defined as the negative pressure change during the initial phase of inspiratory occlusion at a P_{CO_2} of 8 kPa. We considered it useful to present data in terms of changes in apnoeic threshold and slope, the two variables determining the linear ventilatory carbon dioxide response curve.

Finally, concerning the effects of 7-NI, an increase in anaesthetic depth has been observed.[10 11] Our data do not allow inferences to be made regarding this effect, except that it would be hard to reconcile this with the observed large decrease in apnoeic threshold (i.e. a considerable increase in resting $\dot{V}_I$, indicating increased excitability or baseline activity in the central respiratory network).

Combination of 7-NI and morphine

Our data showed that after pretreatment with 7-NI, morphine reduced ventilatory carbon dioxide sensitivity and increased the *X*-intercept of the carbon dioxide response curve (apnoeic threshold). Without 7-NI pretreatment, morphine produces the same effects[14]: the magnitude of the changes in slope and intercept that we found in our study did not differ significantly from those observed previously without 7-NI pretreatment in the same animal preparation (unpaired

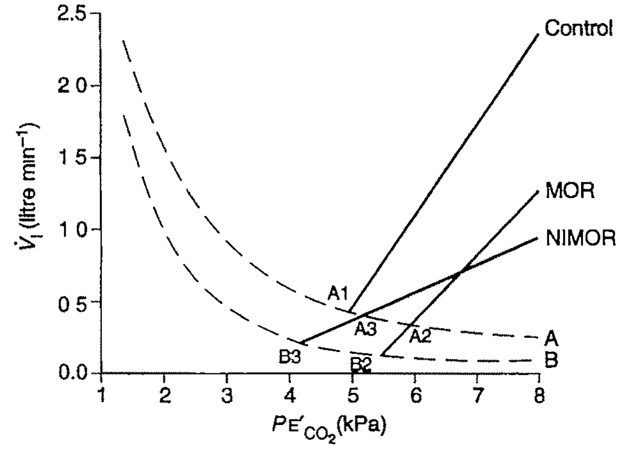


Fig 4 Influence of 7-nitroindazole on morphine-induced ventilatory depression (NIMOR) Hyperbolas A and B are hypothetical metabolic hyperbolas resulting from low (A) or high (B) metabolism Data on the effects of morphine alone (MOR) were calculated after Berkenbosch and colleagues[14] (see text for further explanation).

t tests, $P>0.17$ and $P>0.13$, respectively). Thus the fact that 7-NI does not appear to modify the acute depressant effects of morphine may indicate that the actions of both drugs on V_I are mediated independently of each other. This is supported by our important observation that naloxone, which was given in a dose (0.1 mg kg^{-1}) sufficient to antagonize opioid effects acting at δ, κ and μ receptors,[38] completely abolished all morphine-induced effects but did not reverse the effects already induced by 7-NI. In other words, after infusion of naloxone, all respiratory variables had values which were essentially equal to those after 7-NI treatment, as if no morphine were given (Table 1, Fig. 1).

In this study, we used a linear model to describe the effects of 7-NI, morphine and naloxone on the ventilatory carbon dioxide response curve This model assumes that $P\text{CO}_2$ values are linear below normal for all experimental conditions studied. From our finding that morphine and 7-NI independently influenced G_{tot} and B (no interaction), it follows that the eventual net effect of both treatments on the response curve do not depend on the order in which the drugs are administered.

To answer the question if 7-NI can prevent or reduce morphine-induced respiratory depression, it would be more appropriate to consider a closed loop situation (i.e. a spontaneously breathing subject not exposed to carbon dioxide inhalation), where the metabolic hyperbola and carbon dioxide response curve meet. First, we assume that neither 7-NI nor morphine changed the resting metabolic rate (see metabolic hyperbola A in Fig. 4). Point A1 in Figure 4 is the resting condition. The line NIMOR shows the carbon dioxide response curve after combined 7-NI and morphine administration (note that we also assume linearity of the carbon dioxide response curve at $P\text{CO}_2$ values below normal). Point A3 represents ventilation and P_{CO_2} after combined 7-NI and morphine treatment. Compared with changes after morphine alone (point A2 represents the situation after morphine alone; line MOR was plotted using our previous data[14]), the combined treatment would cause a minor change in ventilation and P_{CO_2} only. However, if morphine decreased the metabolic rate (metabolic hyperbola B in Fig. 3), the situation becomes more complicated. Combined 7-NI and morphine treatment would now result in a substantially larger decrease in ventilation but also in a *decrease* in P_{CO_2} (point B3). Morphine alone would cause an approximately equal or slightly larger ventilatory depression and an increase in P_{CO_2} (point B2). Figure 4 shows that the ability of 7-NI to prevent or reduce the depressant effect of morphine on ventilation depends on the initial situation (metabolic rate, carbon dioxide sensitivity and resting ventilation), and on the effect of both drugs on the carbon dioxide response curve and/or metabolic hyperbola.

In summary, we showed that 7-NI and morphine had independent and partly opposing effects on the control of breathing in the anaesthetized cat The ability of 7-NI to reduce the ventilatory effects of morphine in individual animals depends on its initial condition (for example metabolism, carbon dioxide sensitivity and apnoeic threshold) and on the effects of each drug on the carbon dioxide response curve.

References

1 Moore PK, Wallace P, Gaffen Z, Hart SL, Babbedge RC. Characterization of the novel nitric oxide synthase inhibitor 7-nitroindazole and related indazoles. antinociceptive and cardiovascular effects. *Br J Pharmacol* 1993; **110**: 219–24

2 Moore PK, Babbedge RC, Wallace P, Gaffen ZA, Hart SL. 7-Nitroindazole, an inhibitor of nitric oxide synthase, exhibits anti-nociceptive activity in the mouse without increasing blood pressure. *Br J Pharmacol* 1993; **108**: 296–7

3 Moore PK, Oluyomi AO, Babbegde P, Wallace P, Hart SL. L-N^G-nitro arginine methyl ester exhibits antinociceptive activity in the mouse. *Br J Pharmacol* 1991, **102**· 198–202

4 Przewocki R, Machelska H, Przewocka B. Inhibition of nitric oxide synthase enhances morphine antinociception in the rat spinal cord *Life Sci* 1993; **53**. PL–5

5 Babey AM, Kolesnikov Y, Cheng J, Inturrisi CE, Trifilletti RR, Pasternak GW. Nitric oxide and opioid tolerance. *Neuropharmacology* 1994; **33**: 1463–70

6 Majeed NH, Przewlocka B, Machelska H, Przewlocki R. Inhibition of nitric oxide synthase attenuates the development of morphine tolerance and dependence in mice. *Neuropharmacology* 1994; **33**: 189–92

7 Vaupel DB, Kimes AS, London ED. Comparison of 7-nitroindazole with other nitric oxide synthase inhibitors as attenuators of opioid withdrawal. *Psychopharmacology* 1995; **118**· 361–8

8 Bhargava H, Bian JT, Kumar S Mechanism of attenuation of morphine antinociception by chronic treatment with L-arginine *J Pharmacol Exp Ther* 1997; **281**: 707–12

9 Brignola G, Calignano A, Di Rosa M Modulation of morphine antinociception in the mouse by endogenous nitric oxide *Br J Pharmacol* 1994; **113**: 1372–6

10 Johns RA, Moscicki JC, DiFazio CA. Nitric oxide synthase inhibitor

dose-dependently and reversibly reduces the threshold for halothane anesthesia. *Anesthesiology* 1992; **77**: 779–84

11 Pajewski TN, Difazio CA, Moscicki JC, Johns RA. Nitric oxide synthase inhibitors 7-nitroindazole and nitro-G-L-arginine methyl ester, dose dependently reduce the threshold for isoflurane anesthesia *Anesthesiology* 1996; **85**: 1111–19

12 Pelligrino DA, Laurito CE, VadeBoncouer TR. Nitric oxide synthase inhibition modulates the ventilatory depressant and antinociceptive actions of fourth ventricular infusions of morphine in the awake dog. *Anesthesiology* 1996; **85**· 1367–77

13 Teppema LJ, Berkenbosch A, Olievier CN. Effect of N^{ω}-nitro-L-arginine on ventilatory response to hypercapnia in anesthetized cats. *J Appl Physiol* 1997; **82**: 292–7

14 Berkenbosch A, Teppema LJ, Olievier CN, Dahan A. Influences of morphine on the ventilatory response to isocapnic hypoxia. *Anesthesiology* 1997; **86**. 1342–9

15 DeGoede J, Berkenbosch A, Ward DS, Bellville JW, Olievier CN. Comparison of chemoreflex gains obtained with two different methods in cats. *J Appl Physiol* 1985; **59**: 170–9

16 DeGoede J, Berkenbosch A, Olievier CN, Quanjer PH. Ventilatory response to carbon dioxide and apneic thresholds. *Respir Physiol* 1981; **45**: 185–99

17 Pelligrino DA, Koenig HM, Albrecht RF. Nitric oxide synthesis and regional cerebral blood flow responses to hypercapnia and hypoxia in the rat. *J Cereb Blood Flow Metab* 1993; **13**: 80–7

18 Sandor P, Komjati K, Reivich M, Nyary I. Major role of nitric oxide in the mediation of regional CO_2 responsiveness of the cerebral and spinal cord vessels of the cat. *J Cereb Blood Flow Metab* 1994; **14**: 49–58

19 Faraci FM, Brian JE Jr. 7-Nitroindazole inhibits brain nitric oxide synthase and cerebral vasodilatation in response to N-methyl-D-aspartate. *Stroke* 1995; **26**: 2172–5

20 Smith JJ, Lee JG, Hudetz AG, Hillard CJ, Bosnjak ZJ, Kampine JP. The role of nitric oxide in the cerebrovascular response to hypercapnia. *Anesth Analg* 1997; **84**: 363–9

21 Kelly PA, Ritchie IM, Arbuthnott GW. Inhibition of neuronal nitric oxide synthase by 7-nitroindazole: effects upon local cerebral blood flow and glucose use in the rat. *J Cereb Blood Flow Metabol* 1995; **15**: 766–73

22 Wang Q, Pelligrino DA, Baughman VL, Koenig HM, Albrecht RF. The role of neuronal nitric oxide synthase in the regulation of cerebral blood flow in normocapnia and hypercapnia in rats. *J Cereb Blood Flow Metab* 1995; **15**. 774–8

23 Garthwaite J. Glutamate, nitric oxide and cell signalling in the nervous system. *Trends Neurosci* 1991; **14**· 60–7

24 Snyder SH. Nitric oxide: first in a new class of neurotransmitters. *Science* 1992; **257**: 494–6

25 Garthwaite J, Garthwaite G, Palmer RMJ, Moncada S. NMDA receptor activation induces nitric oxide synthesis from arginine in brain slices. *Eur J Pharmacol* 1989; **172**: 413–16

26 Shintani F, Kanba S, Nakaki T, et *al*. Measurement by in vivo brain microdialysis of nitric oxide release in the rat cerebellum. *J Psychiatry Neurosci* 1994; **19**: 217–21

27 Teppema LJ, Veening JG, Kranenburg A, Dahan A, Berkenbosch A, Olievier CN. Expression of c-fos in the rat brainstem after exposure to hypoxia and to normoxic and hyperoxic hypercapnia. *J Comp Neurol* 1997; **388**: 169–90

28 Vincent SR, Kumura H. Histochemical mapping of nitric oxide synthase in the rat brain. *Neuroscience* 1992; **46**: 755–84

29 Iadecola C, Faris PL, Hartman BK, Xu X. Localization of NADPH diaphorase in neurons of the rostral ventral medulla: possible role of nitric oxide in central autonomic regulation and oxygen chemoreception. *Brain Res* 1993; **603**: 173–9

30 Dun NJ, Dun SL, Forstermann U. Nitric oxide synthase immunoreactivity in rat pontine medullary neurons. *Neuroscience* 1994; **59**: 429–45

31 Chugh DK, Katayama A, Mokashi A, Bebout DE, Ray DK, Lahiri S. Nitric oxide related inhibition of carotid chemosensory nerve activity in the cat. *Respir Physiol* 1994; **97**: 147–56

32 Gozal D, Gozal E, Gozal YM, Torres JE. Nitric oxide isoforms and peripheral chemoreceptor stimulation in conscious rats. *Neuroreport* 1996; **7**: 1145–8

33 Haxhiu MA, Chang CH, Dreshaj IA, Erokwu B, Prabhakar NR, Cherniack NS. Nitric oxide and ventilatory response to hypoxia. *Respir Physiol* 1995; **101**: 257–66

34 Mizusawa A, Ogawa H, Kikuchi W, *et al*. In vivo release of glutamate in nucleus tractus solitarius of the rat during hypoxia. *J Physiol Lond* 1994; **478**: 55–65

35 Ogawa H, Mizusawa A, Kikuchi Y, Hida W, Miki H, Shirato K. Nitric oxide as a retrograde messenger in the nucleus tractus solitarii of rats during hypoxia. *J Physiol Lond* 1995; **486**. 495–504

36 Gozal D, Torres JE, Gozal YM, Littwin SM. Effect of nitric oxide synthase inhibition on cardiorespiratory responses in the conscious rat. *J Appl Physiol* 1996; **81**: 2068–77

37 Patel GM, Horstman DJ, Adams JM, Rich GF. Nitric oxide synthase inhibitors alter ventilation in isoflurane anesthetized rats. *Anesthesiology* 1998; **88**. 1240–8

38 Santiago TV, Edelman NH. Opioids and breathing. *J Appl Physiol* 1985; **59**· 1675–85

British Journal of Anaesthesia **84** (2) 197–203 (2000)

Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia

W. A. C. Mutch*, G. M. Eschun, S. E. Kowalski, M. R. Graham, L. G. Girling and G. R. Lefevre

Department of Anaesthesia and Neuroanaesthesia Research Laboratory, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

**Corresponding author: Department of Anaesthesia, St Boniface General Hospital, 409 Taché Avenue, Winnipeg, Manitoba, R2H 2A6, Canada*

We have studied the time course of changes in gas exchange and respiratory mechanics using two different modes of ventilation during 7 h of isoflurane anaesthesia in pigs. One group received conventional control mode ventilation (CV). The other group received biologically variable ventilation (BVV) which simulates the breath-to-breath variation in ventilatory frequency (*f*) that characterizes normal spontaneous ventilation. After baseline measurements with CV, animals were allocated randomly to either CV or BVV ($F_{I_{O_2}}$ 1.0 with 1.5% end-tidal isoflurane). With BVV, there were 376 changes in *f* and tidal volume (V_T) over 25.1 min. Ventilation was continued over the next 7 h and blood gases and respiratory mechanics were measured every 60 min. The modulation file used to control the ventilator for BVV used an inverse power law frequency distribution ($1/f^a$ with a=2.3±0.3). After 7 h, at a similar delivered minute ventilation, significantly greater Pa_{O_2} (mean 72.3 (SD 4.0) *vs* 63.5 (6.5) kPa) and respiratory system compliance (1.08 (0.08) *vs* 0.92 (0.16) ml cm H_2O^{-1} kg^{-1}) and lower Pa_{CO_2} (6.5 (0.7) *vs* 8.7 (1.5) kPa) and shunt fraction (7.2 (2.7)% *vs* 12.3 (6.2)%) were seen with BVV, with no significant difference in peak airway pressure (16.3 (1.2) *vs* 15.3 (3.7) cm H_2O). A deterioration in gas exchange and respiratory mechanics was seen with conventional control mode ventilation but not with BVV in this experimental model of prolonged anaesthesia.

Br J Anaesth 2000; **84**: 197–203

Keywords: anaesthesia, general; lung, atelectasis; lung, mechanics; ventilation, mechanical; oxygen, partial pressure; pig

Accepted for publication. September 6, 1999

Impaired gas exchange and respiratory mechanics are well known consequences of anaesthesia.[1 2] Up to 90% of patients show deterioration in arterial oxygenation, increased shunt fraction and decreased respiratory system compliance during anaesthesia, which increases over time.[1] Bendixen, Hedley-Whyte and Laver first proposed that atelectasis contributes to this phenomenon.[3] Using computed tomography, Hedenstierna and colleagues showed that impaired gas exchange during anaesthesia was associated with atelectasis in dependent lung areas [1 2 4 5]

Recent work has shown that an 'alveolar recruitment strategy' can improve arterial oxygenation during general anaesthesia.[6] By combining increasing levels of PEEP up to 15 cm H_2O and tidal volumes up to 18 ml kg^{-1}, they demonstrated improved arterial oxygenation after 40 min of anaesthesia. However, others have shown that PEEP may worsen gas exchange during anaesthesia.[7] Alternative approaches, such as intermittent 'sighs' to prevent deterioration in gas exchange during anaesthesia, have been largely unsuccessful.[8 9]

Although an alveolar recruitment strategy improved gas exchange during general anaesthesia, peak airway pressures were high (up to 40 cm H_2O) [6] A technique to prevent atelectasis without increasing airway pressure would benefit patients requiring prolonged mechanical ventilation during anaesthesia. We have developed a new mode of mechanical ventilation termed biologically variable ventilation (BVV).[10] This computer-controlled ventilator simulates breath-to-breath variation in ventilatory frequency (*f*) that characterizes normal spontaneous ventilation. In this experiment, changes in *f* resulted in reciprocal changes in tidal volume (V_T)—low *f* associated with large V_T and vice versa. Using BVV, we found improved gas exchange at similar mean airway pressures (*P*aw) and minute ventilation compared with conventional control mode ventilation (CV) in pigs with experimental acute respiratory distress syndrome (ARDS).[10] Improved gas exchange may be caused by the variations in end-inspiratory pressure from the variable V_T.[11] Such pressure variation may enhance the markedly non-linear recruitment of atelectatic regions seen in ARDS.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

We postulated that BVV may also prevent the deterioration in gas exchange that occurs during prolonged anaesthesia with monotonous ventilation. We also felt that BVV would improve gas exchange without the increases in airway pressure seen with other volume recruitment strategies. In this experiment, we compared gas exchange and respiratory mechanics in pigs who underwent ventilation with either BVV or CV during prolonged isoflurane anaesthesia.

Materials and methods

This study was approved by the Committee for Animal Experimentation at the University of Manitoba. The recommendations of the Canadian Council on Animal Care were followed. We planned to study 20 pigs, weighing 20–30 kg, allocated to receive one of the two modes of ventilation using blocked randomization (n=2×10). All pigs received atropine 0.6 mg i.m. and ketamine 10 mg kg^{-1} i.m. for sedation, and isoflurane in oxygen was administered by face mask. While lying supine, the trachea was intubated with a 6.0-mm tracheal tube. Mechanical ventilation with 100% oxygen was started using an Ohio 7000 anaesthesia ventilator at 15 bpm with minute ventilation adjusted to deliver a measured V_T of approximately 10 ml kg^{-1}. End-tidal isoflurane 2.0% was administered during surgical preparation. Lactated Ringer's solution 500 ml was administered i.v. by the end of surgery and then infused at 10 ml kg^{-1} h^{-1} during the experiment. Pancuronium was administered i.v. for neuromuscular block (20 mg at the outset and 10 mg hourly by infusion). Temperature was maintained at 37±1°C by heating pad and radiant heater.

A double-lumen catheter was inserted into the femoral artery for intermittent blood sampling and continuous recording of arterial pressure. A 7.5-French gauge catheter was inserted into the femoral vein and advanced into the right atrium to measure central venous pressure (CVP). A 7.5-French gauge pulmonary artery catheter was inserted via the external jugular vein and advanced until a satisfactory pulmonary capillary wedge pressure (PCWP) was obtained. Pressure transducers were zero referenced to mid-chest level.

After preparation, the animal was allowed to stabilize for 30 min and the isoflurane concentration was reduced to 1.5% end-tidal. Baseline haemodynamic and respiratory measurements were obtained. Haemodynamic measurements included mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), PCWP and CVP. Airway flow was measured using a pneumotachograph (Hans Rudolph Inc., Kansas City, MO, USA) at the proximal end of the tracheal tube. All measurements were recorded continuously on a Gould 2600 oscillograph (Gould Inc., Cleveland, OH, USA) and intermittently by an advanced CODAS (Dataq Instruments Inc., Akron, OH, USA) data acquisition system. Cardiac output was measured intermittently by thermodilution using 5-ml injections of room temperature saline (performed in triplicate and averaged).

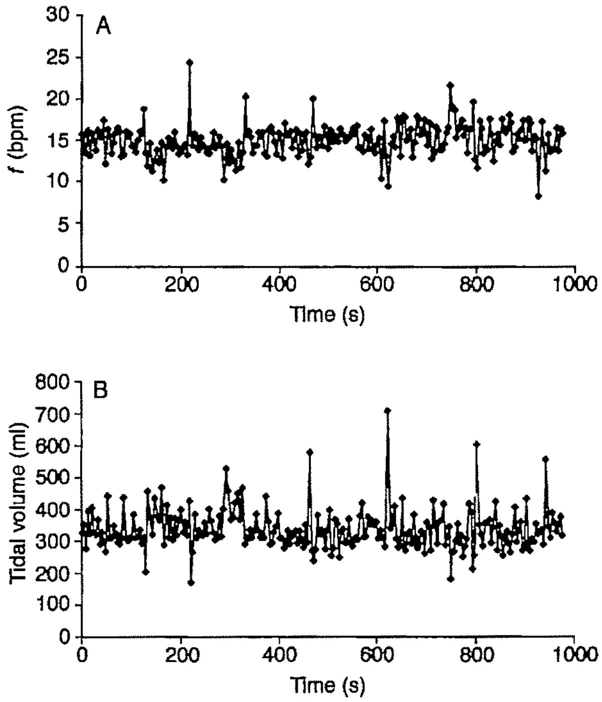


Fig 1 Modulation data used to control ventilatory frequency (*f*) and tidal volume (V_T) with BVV A. Instantaneous *f* (bpm) *vs* time (s) This trace shows 239 consecutive *f* values B Instantaneous V_T vs time seen with the above changes in *f* Mean V_T was 334 ml. Complete fidelity of large V_T with low *f* was not always seen This related to the cycle time between the modulation file output and the mechanical ability of the ventilator to respond with delivery of the largest breaths.

Arterial and mixed venous (sampled from the distal end of the pulmonary artery catheter) blood gases were measured using a Radiometer ABL300 blood-gas analyser (Copenhagen, Denmark). Arterial and mixed venous oxygen content, oxygen saturation and haemoglobin concentrations were measured using a Radiometer OSM3 hemoximeter (Copenhagen, Denmark) set for porcine blood. All measurements were obtained in duplicate. Static respiratory system compliance (*C*rs) was measured over 3–5 breaths by clamping the expiratory limb of the ventilatory circuit at end-inspiration for 0.5–1.0 s to obtain a plateau pressure. Mean values are reported. The V_T used was that which the animal was receiving at the time. This was done so as not to change the mode of ventilation the animal was receiving.

We calculated pulmonary vascular resistance (PVR), shunt fraction (Q_s/Q_t), *C*rs ($\Delta V/\Delta P$), mean airway pressure (*P*aw) and mean peak airway pressure (*P*paw). After these measurements were obtained, a manual forced inspiration was performed (*P*aw 30 cm H_2O for 60 s) to give all animals the same lung volume history. Animals were then allocated randomly to one of two ventilatory modes: conventional IPPV with *f* fixed at 15 bpm (CV group) or IPPV using a computer-controller with variable *f* but with a mean of 15.0 bpm (BVV group). Ventilation continued with either CV or BVV for the duration of the experiment.

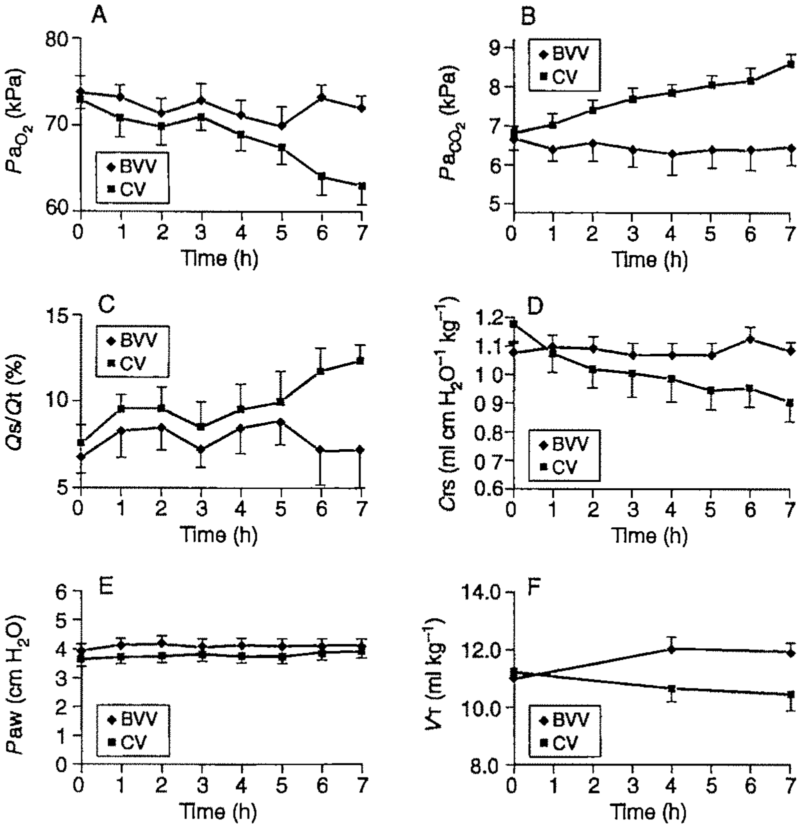


Fig 2 Blood gas and respiratory mechanics for the two experimental groups (mean (SEM)). A. Pa_{O_2} *vs* time for the two experimental groups. Group×time interaction by ANOVA, $P<0.0001$. With BVV, Pa_{O_2} was significantly higher at the end of the study. B: Pa_{CO_2} *vs* time for the two groups. Group×time interaction; $P<0.0001$ With BVV, Pa_{CO_2} was significantly lower. C: Shunt fraction (*Qs/Qt*) *vs* time. Group×time interaction, $P<0.0001$ With BVV, shunt fraction was significantly less. D: Static respiratory system compliance (*Crs*) *vs* time. Group×time interaction, $P<0.0001$. With BVV, *Crs* remained essentially unchanged during the course of the experiment and was significantly decreased with CV. E: Mean airway pressure (*P*aw) *vs* time. Group×time interaction; $P=0.528$ F Measured tidal volume (V_{T_m})/kg *vs* time Group×time interaction, $P=0.0005$ With BVV, measured tidal volume was greater at 4 and 7 h at similar delivered minute ventilation

Every hour for 7 h, haemodynamic and ventilatory data were obtained as above.

The computer-controller and software for the ventilator have been described previously[10] In this instance, the modulation file used to control ventilator *f* and *V*T was generated from an awake animal and scaled to 15 bpm. Briefly, output to control *f* was updated every 5 ms and changed according to the modulation data file. With BVV, *f* varied from 8 to 26 bpm. There were 376 *f* and *V*T combinations over 25.1 min before the modulation file repeated itself. With BVV, *V*T was inversely related to the instantaneous *f* because the ventilator acted as a volume divider. Delivered minute ventilation was not altered.

The data files of airway pressure and volumes were processed to integrate the area under the pressure–time and flow–time curves to give *P*aw and volume. *P*paw was also calculated. Lengthy measurement periods were undertaken to accurately assess measured *f*, *V*T, *P*aw and *P*paw because of the variability in *f* and *V*T after institution of BVV (>120 breaths measured at 4 and 7 h). At the end of each experiment, the animal was killed with a lethal dose of thiopental.

Data were analysed by repeated measures ANOVA. Data are presented as mean (SD), unless otherwise indicated. $P \leq 0.05$ was considered significant for group×time interactions or differences between groups. Least squares means test matrices were generated for *post hoc* comparisons. Bonferroni's correction was applied when multiple comparisons were examined within groups. When an interaction between variables was possible, analysis of covariance was performed. *Post hoc* analysis was as above. Single comparisons between groups were performed using the Student's *t* test; $P \leq 0.05$ was considered significant.

Inverse power law analysis was performed as follows: mean instantaneous *f* was determined (15.0 bpm), then each instantaneous *f* was subtracted from mean *f*; this value was squared and then log transformed. These data were divided into incremental bins of equal size to determine their frequency distribution. The probability of each frequency was determined by *Ni/N* where *Ni*=number of observations in a given frequency bin and *N*=total number of observations. A log transform of the probability distribution was derived. The log probability distribution *vs* log *f* variation was plotted. The confidence interval and correlation coefficient were derived by regression analysis.

Table 1 Haemodynamic data for the two groups (mean (SD)) (n = 8 in each group). MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure, CVP = central venous pressure; CO = cardiac output, and PVR = pulmonary vascular resistance *$P<0.05$ within groups compared with baseline, †$P<0.05$ between groups

	Baseline	1 h	2 h	3 h	4 h	5 h	6 h	7 h
MAP (mm Hg)								
BVV	79.3 (12.5)	81.9 ± 7.5	84.1 ± 8.0	80.6 ± 8.6	76.8 ± 9.2	69.9 ± 8.6	71.9 ± 8.0	67.6 ± 8.3*
CV	83.3 (12.0)	84.8 ± 11.7	84.9 ± 14.0	82.1 ± 16.1	77.3 ± 21	71.9 ± 13.9*	74.8 ± 12.5	69.6 ± 9.6*
MPAP (mm Hg)								
BVV	14.9 (4.9)	15.8 ± 3.3	16.1 ± 4.3	15.4 ± 2.9	15.1 ± 2.9	14.6 ± 2.0	14.8 ± 2.0	15.5 ± 2.4
CV	15.2 (5.0)	16.5 ± 4.0	15.6 ± 3.6	15.4 ± 2.4	15.7 ± 3.0	15.6 ± 1.5	14.5 ± 2.5	15.7 ± 4.3
PCWP (mm Hg)								
BVV	4.6 (1.1)	4.8 ± 1.1	5.2 ± 1.5	4.9 ± 1.2	4.8 ± 1.5	4.5 ± 1.2	4.8 ± 1.4	4.7 ± 1.2
CV	5.7 (0.9)†	6.1 ± 1.7†	6.1 ± 2.0	6.1 ± 1.7†	5.5 ± 1.9	6.1 ± 1.2†	5.0 ± 1.2	5.0 ± 1.1
CVP (mm Hg)								
BVV	2.8 (1.1)	3.3 ± 1.6	2.9 ± 1.4	2.8 ± 2.0	2.9 ± 1.7	2.7 ± 1.5	3.3 ± 1.4	3.5 ± 1.9
CV	3.4 (1.7)	3.7 ± 1.3	3.6 ± 1.1	3.3 ± 1.0	3.3 ± 1.1	3.4 ± 1.5	3.4 ± 1.3	3.3 ± 1.1
CO (litre min^{-1})								
BVV	3.5 (0.9)	3.9 ± 0.9	3.6 ± 0.7	3.7 ± 1.0	3.5 ± 0.9	3.6 ± 0.8	3.6 ± 0.6	3.7 ± 0.4
CV	3.5 (0.6)	4.2 ± 1.0	3.6 ± 0.5	3.6 ± 0.6	3.9 ± 0.6	3.9 ± 0.6	4.2 ± 0.9†	4.3 ± 1.0†
PVR (mm Hg litre min^{-1})								
BVV	3.3 (2.0)	3.0 ± 1.0	3.3 ± 1.4	3.1 ± 1.1	3.2 ± 1.5	3.0 ± 0.9	2.9 ± 0.8	3.0 ± 0.6
CV	2.7 (1.2)	2.5 ± 0.4	3.2 ± 0.5	2.6 ± 0.6	2.8 ± 0.4	2.5 ± 0.4	2.4 ± 0.8	2.5 ± 0.7

Results

We undertook 20 experiments. Three were discarded because of technical problems and one because of suspected hyperthermia. Data were analysed on 16 completed experiments (n=8 in each group).

With BVV, measured mean f was 14.9 (0.2) bpm. A representative recording of changes in f in one experiment is shown in Figure 1A. Mean V_T was 330 (31) ml. Minimal measured V_T was 197 (43) ml and maximal measured V_T was 676 (120) ml, a mean range of 479 ml. A representative recording of the simultaneous changes in V_T with changes in f is shown in Figure 1B. With BVV, mean Ppaw was 16.3 (1.3) cm H_2O. Mean minimal Ppaw (at the lowest mean V_T) was 12.8 (2.1) cm H_2O. Mean maximal Ppaw (at the highest mean V_T) was 25.9 (4.3) cm H_2O.

Haemodynamic data are shown in Table 1. MAP and MPAP were stable, with only small differences within groups over the course of the experiments. There was a significant group×time interaction for PCWP (P=0.043). At baseline, there was a mean difference of 1.1 mm Hg with the greater pressure with CV. At the end of the study, the mean difference was 0.3 mm Hg and this was not significant. In contrast, there was no significant difference in CVP between groups (group×time interaction; P=0.698). At 6 and 7 h, cardiac output was higher in the CV group. Associated with the differences in cardiac output, mixed venous oxygen tension ($P\bar{v}_{O_2}$) was greater in the CV group at 6 and 7 h. There were no differences in PVR between groups.

Table 2 Minute ventilation data in the two groups (mean (SD)). V_{T_d} = delivered tidal volume, V_{T_m} = measured tidal volume; f = ventilatory frequency; and Ppaw = peak airway pressure *$P<0.05$ within groups compared with baseline, †$P<0.05$ between groups

	Baseline	4 h	7 h
V_{T_d} (ml kg^{-1})			
BVV	17.7 (1.9)	17.7 (1.9)	17.7 (1.9)
CV	17.2 (1.0)	17.2 (1.0)	17.2 (1.0)
V_{T_m} (ml kg^{-1})			
BVV	11.0 (0.7)	12.1 (1.4)†	11.9 (1.3)†
CV	11.2 (0.4)	10.6 (0.9)*	10.4 (0.6)*
f (bpm)			
BVV	15.0 (0)	14.9 (0.2)	14.9 (0.2)
CV	15.0 (0)	15.0 (0)	15.0 (0)
Ppaw (cm H_2O)			
BVV	15.4 (1.5)	16.3 (1.5)*	16.3 (1.2)*
CV	14.3 (2.8)	14.8 (2.9)	15.3 (3.7)*

Pa_{O_2} was similar in the two groups at baseline. By 6 h, Pa_{O_2} was significantly greater with BVV (Fig. 2A; group×time interaction; $P<0.0001$). Pa_{CO_2} was similar at baseline (Fig. 2B). At the end of the study, mean Pa_{CO_2} was 2.0 kPa greater with CV (group×time interaction; $P<0.0001$). With BVV, shunt fraction was stable over the course of the experiment. In contrast, shunt fraction increased significantly to 160% of baseline at 7 h with CV (group×time interaction; $P<0.0001$; Fig. 2C). Because shunt fraction, cardiac output[12] and $P\bar{v}_{O_2}$ are related,[13] analysis of covariance was used to compare shunt fraction to correct for differences in cardiac output and $P\bar{v}_{O_2}$ at the later times between groups. Correcting for differences in cardiac output and $P\bar{v}_{O_2}$ at the later times, shunt fractions remained significantly lower with BVV

There was a significantly smaller respiratory system compliance (Fig. 2D) with CV by 4 h (group×time interaction; $P<0.0001$) that persisted for the rest of the experiment. Compliance differed by 19% between groups at the end of the study. There was no group×time interaction for Paw at 4 or 7 h (Fig. 2E; P=0.528).

Table 2 shows minute ventilation data. At baseline, delivered minute ventilation (measured from the back of

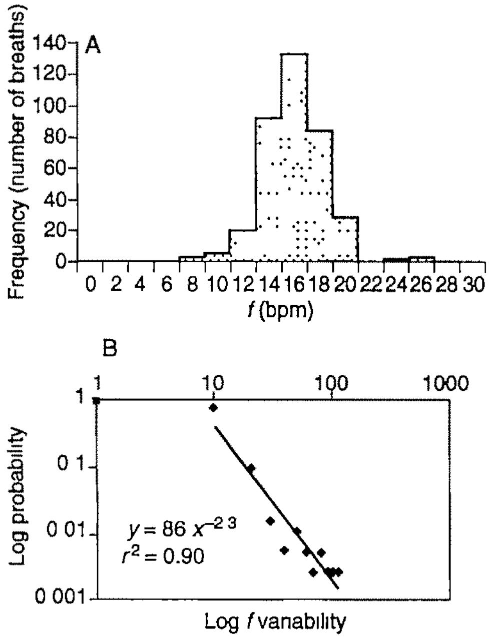


Fig 3 Distribution of *f* for the modulation file used to control the BVV ventilator. A. Frequency distribution of *f* for the modulation file. B: Log–log plot of probability distribution *vs* *f* variability used to program the biologically variable ventilator. A $1/f^a$ plot is obtained with $a=2.3\pm0.3$ The solid box (■) shows the probability distribution with CV The probability is 1 with no *f* variability The *f* variability is shown as 1 because the log of zero variability is undefined. The difference in the behaviour of the two ventilatory modes is clear.

the ventilator), the product of *f* and delivered *V*T (*V*T$_d$) (*f*× *V*T$_d$), was not different between groups and did not change during the experiment. Measured minute ventilation (at the end of the tracheal tube), the product of *f* and measured *V*T (*V*T$_m$) (*f*×*V*T$_m$), did not differ between groups (165 (11) ml kg^{-1} with BVV and 167 (6) ml kg^{-1} with CV) at baseline. At baseline, measured *V*T with control mode ventilation was similar in both groups (11.2 (0.4) ml kg^{-1} with CV and 11.0 (0.7) ml kg^{-1} with BVV; $P=0.616$; Fig. 2F). Differences in the product (*f*×V$_{Tm}$) became apparent with time. Although *f* was unchanged (>120 instantaneous breath intervals were measured per observation with BVV), measured *V*T/kg increased with BVV and decreased with CV. Measured *V*T was approximately 14% greater with BVV. There was no difference between groups for *P*paw (group×time interaction; $P = 0.530$). Within groups, *P*paw increased over time.

The frequency *vs* *f* distribution for the modulation file used to generate BVV is shown in Figure 3A. The probability distribution *vs* *f* variability is shown in Figure 3B. The data followed an inverse power law ($1/f^a$ with $a=2.3\pm0.3$).

Discussion

Normal breathing has considerable variation in rate and volume. This variation is lost with conventional controlled ventilation during anaesthesia. We postulated that loss of respiratory variation contributes to the deterioration in gas exchange and respiratory mechanics during anaesthesia. During prolonged anaesthesia in pigs, we have shown that BVV resulted in better arterial oxygenation, carbon dioxide clearance and compliance, while shunt fraction was lower compared with CV. Such improvements occurred without BVV being a true facsimile of spontaneous breathing. In this study, changes in *f* resulted in reciprocal changes in *V*T as the ventilator functioned as a volume divider. Independent variation in *V*T, although possible with the modified ventilator developed, was not attempted. Incorporating such variability could result in a truer modelling of natural breathing.

At baseline, with both groups undergoing ventilation at a similar minute ventilation in standard control mode, there were no differences for any of the measured variables defining gas exchange or respiratory mechanics. The modulation file used to control BVV output was scaled to provide the same mean *f* as in the control group Thus adding variation in *f* and reciprocal variation in *V*T at unaltered delivered minute ventilation was the only intervention undertaken. Despite identical starting conditions, measured *V*T/kg increased with BVV over time while it decreased with CV. A decrease in measured *V*T would be expected with CV during prolonged anaesthesia as compliance decreases. This is especially so with anaesthesia circuits where the circle system and tubing are relatively compliant (approximately 2 ml cm H_2O^{-1} litre^{-1} in our system). With BVV, a greater fraction of delivered *V*T was used (an increase of 0.9 ml kg^{-1} from baseline; 5% of the 17.7 ml kg^{-1} available). With CV, less of the delivered *V*T entered the lungs (a 3% decline from baseline). The difference in compliance between groups at 7 h (19%) can account for the differences in *V*T. Given the stable gas exchange and respiratory mechanics with BVV, the additional measured *V*T appears favourably distributed, implying superior *V*A/*Q* matching. For instance, by the end of the experiment, mean Pa_{CO_2} was 2.0 kPa greater with CV. This increase in Pa_{CO_2} probably represents an increase in deadspace ventilation with CV over time, given the stable depth of anaesthesia and stable temperature (that is stable metabolism in both groups). At 7 h there was no difference in oxygen consumption between groups (142 (38) ml min^{-1} with CV and 141 (11) ml min^{-1} with BVV), as measured by the Fick equation. However, the statistical power of this finding was low and small changes may have been undetected.

The small differences in *V*T cannot account solely for the differences in gas exchange. Almost doubling mean *V*T resulted in only small improvements in gas exchange during mechanical ventilation[9] Thus the manner in which breaths are delivered appears to be important; increasing *V*T in a monotonous manner seems to be ineffectual. Deterioration in pulmonary function with CV in our experiment is consistent with the well documented changes during prolonged mechanical ventilation under anaesthesia.

In a model of ARDS, we found 12% greater *V*T after 4 h with BVV,[10] with a significant difference in compliance between BVV and CV. In our current experiment, in healthy lungs, compliance remained stable in the BVV group. Failure to show an increase may relate to the way compliance was measured in this experiment (3–5 measurements of static compliance during variable breathing so as not to alter the mode of ventilation). In contrast, there was a significant decrease in compliance in the CV group.

Examination of Figure 1B shows the variation in V_T over time in one experiment. In this example, mean V_T was 334 (63) ml for 239 consecutive breaths over 16.2 min. There was only one breath that exceeded mean V_T by 100% (706 ml) which could be defined as a sigh. The ability of sighs to prevent deterioration in gas exchange during prolonged anaesthesia remains controversial. The important difference between BVV and sighs is that BVV does not affect mean pressure over time because both large and small V_T are delivered. Frequently delivered sighs of volume $\geqslant$100% of mean V_T would result in increased *P*aw and *P*paw over time.

We have not shown that BVV prevents atelectasis. However, shunt fraction correlated with atelectasis, as measured by computed tomography, during anaesthesia (shunt=1.6×atelectatic area+1.7)[14]. If such results apply to this experiment, then atelectasis in animals undergoing ventilation with BVV would not change (+0.1% atelectatic area) compared with an increase of 2.9% atelectatic area with CV.

Based on analysis of our work, Suki and colleagues proposed a theoretical model of how BVV with its noisy or variable *P*paw could better recruit atelectatic lung.[11] The improved gas exchange with BVV could result from stochastic resonance, that is the use of a noisy input (variable end-inspiratory pressure) to enhance output (Pa_{O_2}) in a non-linear system.[15] In our study of severe ARDS, variable ventilation was needed for 1.5–2 h to see improved gas exchange. In this experiment in healthy lungs, advantages were clearly noticeable after only 5 h.

The variation we programmed into our respiratory control files (based on awake or lightly anaesthetized animal breathing patterns) had the characteristics of an inverse power law frequency distribution ($1/f^a$).[16 17] Such inverse power law behaviour is ubiquitous in biological rhythms.[18 19] Frey and colleagues found that the spontaneous breathing patterns of infants follow such power law distributions[20] and suggested that the tonic neural inputs to the respiratory oscillator are noisy. Conventional control mode ventilation (the standard for anaesthesia) eliminates such 'normal' noisy ventilatory patterns (Fig. 3). It is not clear if the variability file chosen for BVV in this experiment was optimal. We have successfully used variations with a=1.5–2.5. Frey and colleagues found that a=3.2 in term infants.[20] A greater a-value is associated with a smaller probability of large variations in *f*. Airway impedance in humans varies with a=1.5–2.5.[21] Suki and colleagues showed that the incremental avalanche-like recruitment of lung volume, the timing of such recruitment and the changes in airway impedance with such recruitment followed inverse power law behaviour with negative slopes from 1.1 to 2.5.[22 23] Inverse power law behaviour can define many features of pulmonary mechanics and gas exchange, and the noise programmed in this experiment appears to be within the range of 'noise' seen with other respiratory variables. Importantly, the respiratory variation used with BVV is not random ($1/f^a$ with a=0 or white noise).

Simulation of another physiological phenomenon, respiratory sinus arrhythmia, the normal changes in spontaneous heart rate with the phases of respiration, improves pulmonary gas exchange and circulatory efficiency.[24] In anaesthetized dogs, respiratory sinus arrhythmia induced by pacing the diaphragm and concurrently stimulating the vagus nerve during expiration improved shunt fractions and decreased deadspace ventilation compared with constant stimulation or vagal stimulation during inspiration. Respiratory and heart rates can become phase locked which can increase the effects of respiratory sinus arrhythmia.[25 26] BVV, by returning normal variation in ventilatory frequency, has resulted in some of the improvements in pulmonary gas exchange described in the experiment by Hayano and colleagues.[24]

Further refinements in breathing variation are possible with independent control of *f* and V_T, an obvious choice to start to more closely mimic normal breathing.

The better gas exchange and pulmonary mechanics with BVV in this study were similar to results obtained in our studies of ARDS. Those studies showed a therapeutic benefit of BVV. This study suggests a prophylactic benefit and indicates that BVV may be a superior mode for controlled ventilation during anaesthesia. Whether this is the case clinically must await further study.

Acknowledgements

We thank Barb Robson for excellent technical assistance and Mary Cheang (M Math) for statistical analysis. The study was supported by the Crocus Investment Fund and the Industrial Research Assistance Program. Some of the concepts discussed are protected by US Patent No. 5,647,350, 'Control of Life Support Systems', owned by Biovar Life Support Inc, jointly held by Drs W. A. C. Mutch, G R Lefevre, University of Manitoba and the Crocus Investment Fund

References

1 Hedenstierna G. Gas exchange pathophysiology during anesthesia. In: Breen PH, ed. *Anesthesiology Clinics of North America*. Philadelphia: WB Saunders, 1998, 113–27

2 Hedenstierna G. Ventilation–perfusion relationships during anaesthesia. *Thorax* 1995; **50**: 85–91

3 Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: A concept of atelectasis. *N Engl J Med* 1963; **269**: 991–6

4 Hachenberg T, Lundquist H, Tokics L, Brismar B, Hedenstierna G. Analysis of lung density by computed tomography before and during general anaesthesia. *Acta Anaesthesiol Scand* 1993; **37**: 549–55

5 Reber A, Engberg G, Sporre B, *et al.* Volumetric analysis of

aeration in the lungs during general anaesthesia. *Br J Anaesth* 1996; **76**: 760–6

6 Tusman G, Böhm SH, Vazquez de Anda GF, do Campo JL, Lachmann B. 'Alveolar recruitment strategy' improves arterial oxygenation during general anaesthesia *Br J Anaesth* 1999; **82**: 8–13

7 Hewlett AM, Hulands GH, Nunn JF, Milledge JS. Functional residual capacity during anaesthesia. III: Artificial ventilation. *Br J Anaesth* 1974; **46**: 495–503

8 Balsys AJ, Jones RL, Man SFP, Wells A. Effects of sighs and different tidal volumes on compliance, functional residual capacity and arterial oxygen tension in normal and hypoxemic dogs. *Crit Care Med* 1980; **8**. 641–5

9 Levine M, Gilbert R, Auchincloss JH. A comparison of the effects of sighs, large tidal volumes, and positive end expiratory pressure in assisted ventilation. *Scand J Respir Dis* 1972; **53**: 101–8

10 Lefevre GR, Kowalski SE, Girling LG, Thiessen DB, Mutch WAC Improved arterial oxygenation after oleic acid lung injury in the pig using a computer-controlled mechanical ventilator. *Am J Respir Crit Care Med* 1996; **154**: 1567–72

11 Suki B, Alencar AM, Sujeer MK, *et al.* Life-support system benefits from noise. *Nature* 1998; **393**: 127–8

12 Lynch JP, Mhyre JG, Dantzker DR Influence of cardiac output on intrapulmonary shunt. *J Appl Physiol* 1979, **46**: 315–21

13 Sandoval J, Long GR, Skoog C, Wood LDH, Oppenheimer L. Independent influence of blood flow rate and mixed venous PO_2 on shunt fraction. *J Appl Physiol* 1983; **55**: 1128–33

14 Gunnarsson L, Tokics L, Gustavsson H, Hedenstierna G. Influence of age on atelectasis formation and gas exchange impairment during general anaesthesia *Br J Anaesth* 1991; **66**: 423–32

15 Wiesenfeld K, Moss F. Stochastic resonance and the benefits of noise: From ice ages to crayfish and SQUIDs. *Nature* 1995; **373**. 33–6

16 West B, Goldberger A. Physiology in fractal dimensions. *Am Sci* 1987; **75**: 354–65

17 West BJ, Shlesinger M. The noise in natural phenomena. *Am Sci* 1990; **78**: 40–5

18 Pagani M, Lombardi F, Guzzetti S, *et al* Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986, **59**: 178–93

19 Rimoldi O, Pierini S, Ferrari A, Cerutti S, Pagani M, Malliani A. Analysis of short-term oscillations of R-R and arterial pressure in conscious dogs. *Am J Physiol* 1990; **258**: H967–76

20 Frey U, Silverman M, Barabási A-L, Suki B. Irregularities and power law distributions in the breathing pattern in preterm and term infants *J Appl Physiol* 1998; **86**: 789–97

21 Que C-L, Kenyon CM, Maksym G, Olivenstein R, Macklem PT Equilibrium, homeostasis, and complexity. *Ann RCPSC* 1998; **31**: 194–200

22 Barabási A-L, Buldyrev SV, Stanley HE, Suki B. Avalanches in the lung: A statistical mechanical model *Phys Rev Lett* 1996; **76**: 2192–5

23 Suki B, Barabási A, Hantos Z, Peták F, Stanley HE. Avalanches and power-law behaviour in lung inflation *Nature* 1994, **368**: 615–18

24 Hayano J, Yasuma F, Okada A, Mukai S, Fujinami T. Respiratory sinus arrhythmia: A phenomenon improving pulmonary gas exchange and circulatory efficiency. *Circulation* 1996; **94**: 842–7

25 Galletly DC, Larsen PD. Cardioventilatory coupling during anaesthesia. *Br J Anaesth* 1997; **79**. 35–40

26 Galletly DC, Larsen PD. Relationship between cardioventilatory coupling and respiratory sinus arrhythmia *Br J Anaesth* 1998, **80**: 164–8

British Journal of Anaesthesia 84 (2). 204–14 (2000)

Fentanyl protects the heart against ischaemic injury via opioid receptors, adenosine A_1 receptors and K_{ATP} channel linked mechanisms in rats

R. Kato*, S. Ross and P. Foëx

Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE, UK

**Corresponding author*

We have investigated if fentanyl protects against myocardial ischaemic injury and if so, if the mechanism of this protection is mediated via opioid and adenosine A_1 receptors, and K_{ATP} channels. Langendorff rat hearts were subjected to global ischaemia (30 min) and reperfusion (60 min). The drugs were administered before induction of ischaemia and maintained throughout the experiment. Treatment with fentanyl 740 nmol $litre^{-1}$ improved post-ischaemic mechanical function, assessed as developed pressure, +d*P*/dtmax and –d*P*/dtmin, compared with controls after 60 min of reperfusion. These effects were abolished by naloxone 1 μmol $litre^{-1}$, DPCPX 10 μmol $litre^{-1}$, a selective adenosine A_1 antagonist and sodium 5-hydroxydecanoate 100 μmol $litre^{-1}$, a K^+_{ATP} channel blocker. We conclude that fentanyl protected the heart against post-ischaemic injury by a mechanism which was blocked by an opioid and an adenosine A_1 receptor antagonist and also by a K_{ATP} channel antagonist.

Br J Anaesth 2000; **84**: 204–14

Keywords: analgesics opioid, fentanyl; ions, potassium; ions, ion channels, potassium; receptors, opioid; receptors, adenosine; heart, ischaemia; rat

Accepted for publication: September 2, 1999

Transient myocardial ischaemia may occur during anaesthesia and surgery. Myocardial performance is compromised to a variable degree after ischaemia and subsequent reperfusion. This dysfunction reflects either irreversible (infarction) or reversible injury. The latter is often termed myocardial stunning where dysfunction persists despite return of full perfusion. Recovery of this dysfunction is facilitated by some drugs, including halogenated anaesthetics.[1–4] In many models investigating this improvement, the protective drug is given before the ischaemic insult and, therefore, may act by preconditioning. This term was originally coined for the protection which brief periods of ischaemia confer on the heart against subsequent damage caused by prolonged ischaemia.[5] This phenomenon, 'ischaemic' preconditioning, has been investigated extensively because of its clinical relevance and scientific interest. Several mediators are involved in myocardial preconditioning, including protein kinase C (PKC) and ATP-sensitive potassium channels (K_{ATP} channels).[6 7] The existence of mediators has suggested the possibility for novel interventions which would represent 'pharmacological' preconditioning; protection could be induced by administering drugs which activate effectors intervening in ischaemic preconditioning before the ischaemic period, and serve the same purpose as brief ischaemic episodes.

Opioids are linked to PKC[8–10] and are therefore putative mediators in preconditioning.[6 7 10] Indeed, opioid receptor agonists have been shown to protect the heart from the insult of ischaemia. Administration of morphine before an ischaemic insult mimics ischaemic preconditioning and protects against infarction in anaesthetized rats[11 12] and in isolated rat hearts.[13] Furthermore, the opioid antagonist naloxone abolishes ischaemic preconditioning.[14 15] However, there has been little work on the protective effects which activation of the opioid system may confer against contractile dysfunction which occurs after brief periods of ischaemia.

Adenosine is released endogenously from the myocardium during ischaemia and reperfusion, and alleviates ischaemic damage.[16] Exogenous adenosine receptor agonists have been shown to protect against injury in various myocardial ischaemia models.[3 17 18] Several mechanisms have been postulated for their protective action, including inhibition of norepinephrine release from sympathetic nerve endings and attenuation of production of free radicals and calcium influx into reperfused myocardium.[19 20] There is convincing evidence to suggest involvement of adenosine receptors in ischaemic preconditioning. Adenosine A_1 receptors share with opioid receptors a common cellular pathway linked to PKC,[21] and an adenosine A_1 blocker abolishes

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

the cardiac protection induced by ischaemic preconditioning.[22 23] Furthermore, protective effects by activating α_1 adrenergic receptors, equivalent to opioid receptors in the PKC activation pathway,[6 7] have been blocked by an adenosine A_1 antagonist,[24 25] suggesting that adenosine may be a key effector in pharmacologically induced preconditioning.

K_{ATP} channels are activated as a result of a decrease in the level of intracellular ATP, and are well characterized in myocytes.[26] Although the role of enhancement of K^+ conductance in the progression of ischaemic damage remains unknown, activation of this channel is without doubt involved in the protection against myocardial ischaemic injury. Opening of this channel has been shown repeatedly to facilitate recovery of mechanical function[27 28] and decrease infarct size after ischaemia.[29] The well known protection exerted by halogenated anaesthetics against stunning is mediated by activation of K_{ATP} channels.[30 31] Of further interest is the fact that PKC activates K_{ATP} channels.[32] These channels are regarded as the end-effector in ischaemic preconditioning.[6 7]

The purpose of this study was to examine if administration of fentanyl protects against post-ischaemic mechanical dysfunction, and if protection was evident, to determine if an opioid receptor antagonist, an A_1 adenosine receptor antagonist or a K_{ATP} channel blocker could prevent this protection. Fentanyl was chosen because it is used widely in clinical practice, including the management of patients with ischaemic heart disease, and its protective potential has not been investigated.

Materials and methods

The study was performed in accordance with the UK Animal Act (scientific procedures) 1986 (Home Office licence number 30/00980).

Preparation of rat hearts

Adult male Wistar rats (325–400 g) were anaesthetized with pentobarbital 60 mg kg^{-1} i.p. The hearts were excised rapidly, arrested in ice-cooled Krebs–Henseleit buffer, and perfused retrogradely through the aorta using a Langendorff apparatus. The Krebs–Henseleit perfusion solution (containing (mmol $litre^{-1}$) NaCl 118.7, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 0.95, $NaHCO_3$ 28, $CaCl_2$ 1.3 and glucose 10) was filtered through a 5.0 µm filter, oxygenated with a mixture of 95% oxygen and 5% carbon dioxide, and maintained at 37°C throughout the procedure. pH was 7.4 when equilibrated with carbon dioxide at 37°C. Perfusion pressure was set at 100 cm H_2O and kept constant.

The left and right ventricles were vented by apical puncture with a polyethylene drain and ventriculotomy, respectively. A latex balloon, slightly larger than the ventricle, was inserted through the left atrium into the left ventricle and connected by a polyethylene catheter to a saline-filled syringe and to a pressure transducer (Medex Medical Inc, Lancashire, UK). All hearts were paced with right ventricular epicardial electrodes at a fixed rate of 5 Hz (2 ms, 5 V square pulses). The volume of the balloon was adjusted to achieve an end-diastolic pressure (EDP) of 5–10 mm Hg which remained unchanged throughout the study.

After a stabilization period of 10 min, only those hearts that met the following criteria were studied: peak systolic pressure (PSP) >85 mm Hg; EDP <10 mm Hg; and coronary flow (CF) >12.0 ml min^{-1}.

Experimental design

Hearts were allocated to one of 18 groups.

Non-ischaemia study

There were six groups in this study. The hearts in these groups did not undergo ischaemia. Group NI-Fent was treated with fentanyl ($n=5$), group NI-Nal with the non-selective opioid receptor antagonist naloxone ($n=5$), group NI-HD with the K_{ATP} channel blocker sodium 5-hydroxydecanoate (5-HD) ($n=5$), group NI-Veh with the vehicle dimethyl sulphoxide (DMSO) ($n=5$), group NI-DPC with the adenosine A_1 antagonist 1,3-depropyl-8-cyclopentylxanthine (DPCPX) ($n=5$) and group NI-Cont with no drug.

Ischaemia study 1

There were 10 groups according to which drug(s) was administered. Group Fent was treated with fentanyl ($n=7$), group Nal with naloxone ($n=6$), group HD with 5-HD ($n=5$), group Veh with DMSO ($n=6$), group DPC with DPCPX ($n=6$), group Fent+Nal with fentanyl and naloxone ($n=7$), group Fent+HD with fentanyl and 5-HD ($n=5$), group Fent+Veh with fentanyl and DMSO ($n=5$) and group Fent+DPC with fentanyl and DPCPX ($n=6$). The control group (Cont) ($n=8$) received no drug treatment.

Ischaemia study 2

The hearts were allocated to one of two groups depending on the period of fentanyl incubation before ischaemia. Group Fent10 ($n=7$) was perfused with fentanyl for 10 min and group Fent15 ($n=6$) for 15 min.

Concentrations of the drugs were fentanyl 740 nmol $litre^{-1}$ (Janssen-Cilag Ltd, Buckinghamshire, UK), naloxone 1 µmol $litre^{-1}$ (Du Pont Pharmaceuticals Ltd, Hertfordshire, UK), 5-HD 100 µmol $litre^{-1}$ (Sigma-Aldrich, Dorset, UK) and DPCPX 10 µmol $litre^{-1}$ (Sigma-Aldrich) (in 0.04% DMSO (Sigma-Aldrich)).

The experimental procedure is summarized in Figure 1. After a period of stabilization (10 min), pre-drug levels of ventricular mechanical function were measured. The appropriate drug was then administered to the perfusate and maintained until the end of the study. In the non-ischaemia study, measurements were obtained at 20, 60, 70, 80, 90, 100 and 110 min after administration of 5-HD in group NI-HD, and at 15, 55, 65, 75, 85, 95 and 105 min after the pre-drug measurement in the remainder of the non-ischaemia

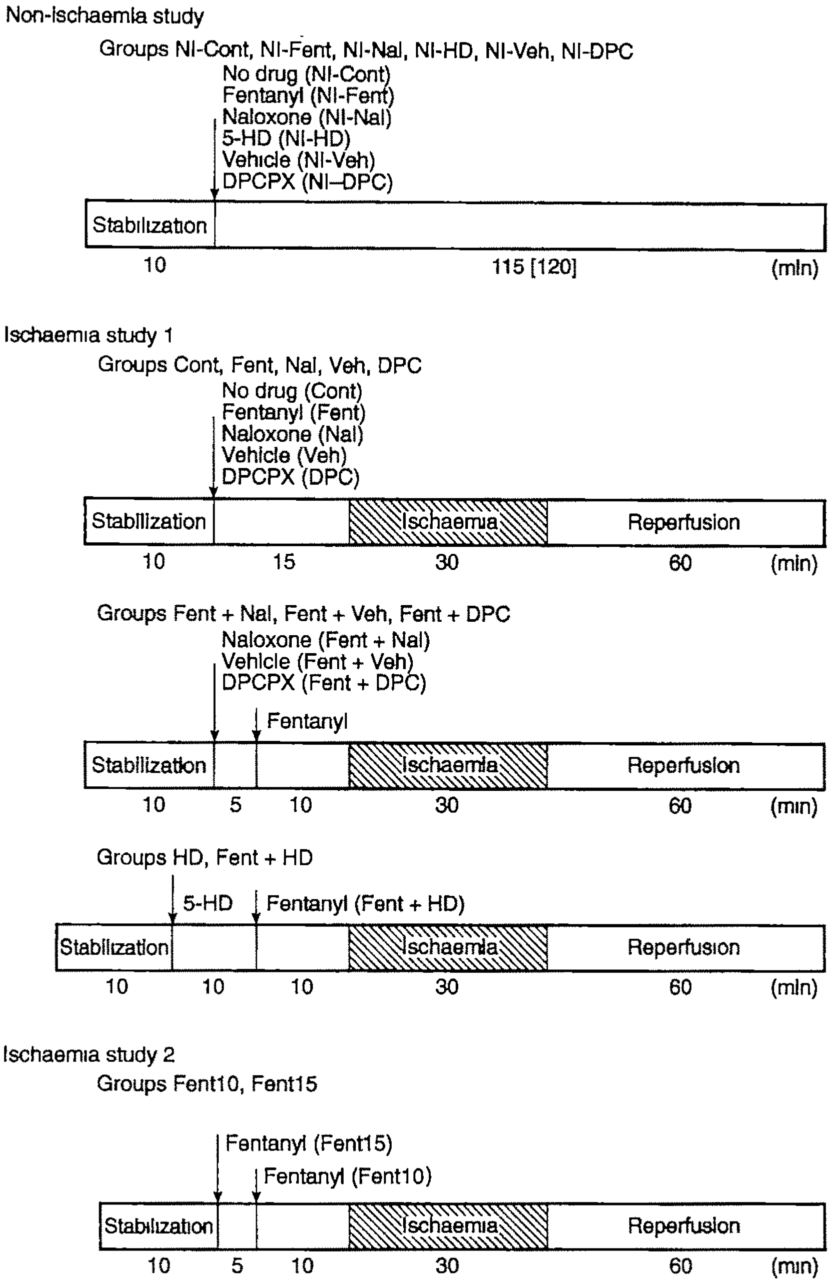


Fig 1 Study design

groups. 5-HD had a longer pre-treatment time so that the results from the non-ischaemia study were comparable with ischaemia study 1 where 5-HD needed an additional 5 min pre-incubation time (see below). In the ischaemia studies, measurements just before ischaemia were taken as pre-ischaemic values. Ischaemia was caused by stopping the flow of the perfusate to the heart, and pacing was stopped at the onset of ischaemia. After 30 min of ischaemia, aortic flow was reintroduced and continued for a further period of 60 min. Pacing was reintroduced 8 min into reperfusion and continued until the end of the study. Measurements were obtained at 10, 20, 30, 40, 50 and 60 min during reperfusion. 5-HD was pre-incubated for 10 min before administration of fentanyl, 5 min longer than the other antagonists. This was because preliminary experiments showed that the effect of fentanyl was not blocked by 5-HD with 5 min pre-incubation (data not shown).

Measurements included PSP, EDP, developed pressure (DP), maximum positive and minimum negative left ventricular pressure derivatives (+d*P*/d*t*max and –d*P*/d*t*min) and CF.

Data collection and analysis

Left ventricular pressure was monitored continuously throughout the experiment. The left ventricular pressure signal was digitized at 250 Hz (analogue–digital converter AT-MIO, National Instruments Corporation, TX, USA) and stored on the hard disk of a desktop computer. Data were

Table 1 Indices of mechanical function in the non-ischaemia study Times in [ ] were used only in group NI-HD. DP=Developed pressure, EDP=end-diastolic pressure, +d*P*/d*t*max=maximum positive left ventricular pressure derivative, –d*P*/d*t*min=minimum negative left ventricular pressure derivative, CF=coronary flow NI=Non-ischaemic, Cont=control (no drug), Fent=fentanyl, Nal=naloxone, HD=5-HD Results are mean (SEM) No differences between groups at any time

		Post-drug (min)						
	Pre-drug	15 [20]	55 [60]	65 [75]	75 [80]	85 [90]	95 [100]	105 [110]
DP (mm Hg)								
NI-Cont	111 (2)	106 (2)	101 (3)	99 (3)	97 (3)	95 (2)	94 (2)	93 (2)
NI-Fent	109 (4)	104 (5)	97 (5)	95 (5)	91 (4)	90 (4)	89 (4)	87 (4)
NI-Nal	110 (3)	102 (2)	97 (2)	96 (2)	92 (2)	91 (2)	90 (2)	89 (2)
NI-HD	112 (5)	104 (5)	98 (5)	94 (4)	94 (4)	94 (4)	93 (4)	92 (4)
NI-Veh	109 (5)	102 (5)	96 (5)	96 (4)	95 (4)	93 (3)	93 (3)	91 (3)
NI-DPC	108 (5)	100 (3)	94 (4)	93 (3)	93 (3)	92 (3)	91 (3)	89 (3)
EDP (mm Hg)								
NI-Cont	6 (0)	5 (0)	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)	4 (0)
NI-Fent	5 (1)	5 (1)	5 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)
NI-Nal	5 (0)	4 (1)	4 (1)	3 (1)	3 (0)	3 (0)	3 (0)	3 (0)
NI-HD	6 (1)	4 (1)	4 (1)	3 (1)	3 (1)	3 (0)	3 (0)	3 (0)
NI-Veh	5 (1)	4 (1)	4 (1)	3 (1)	3 (0)	3 (0)	3 (0)	3 (0)
NI-DPC	5 (0)	5 (0)	5 (0)	5 (0)	4 (0)	4 (0)	4 (0)	5 (0)
+d*P*/d*t*max (mm Hg s^{-1})								
NI-Cont	2801 (84)	2731 (81)	2576 (78)	2503 (96)	2522 (95)	2467 (84)	2442 (85)	2414 (90)
NI-Fent	2873 (113)	2740 (85)	2680 (75)	2592 (68)	2504 (56)	2440 (81)	2400 (94)	2414 (86)
NI-Nal	2985 (113)	2773 (82)	2663 (87)	2600 (82)	2532 (98)	2519 (100)	2509 (106)	2500 (113)
NI-HD	2858 (130)	2701 (120)	2562 (113)	2527 (96)	2451 (105)	2434 (104)	2403 (111)	2377 (125)
NI-Veh	2852 (107)	2644 (138)	2514 (154)	2510 (128)	2442 (103)	2396 (103)	2371 (102)	2368 (91)
NI-DPC	2790 (127)	2631 (115)	2553 (87)	2502 (78)	2465 (87)	2421 (90)	2402 (94)	2386 (95)
–d*P*/d*t*min (mm Hg s^{-1})								
NI-Cont	1994 (98)	1903 (102)	1802 (91)	1737 (74)	1708 (101)	1656 (82)	1640 (85)	1633 (70)
NI-Fent	2042 (62)	1936 (63)	1891 (65)	1828 (70)	1778 (91)	1749 (75)	1728 (70)	1716 (77)
NI-Nal	1978 (68)	1875 (76)	1826 (80)	1816 (108)	1748 (86)	1734 (88)	1637 (87)	1638 (84)
NI-HD	1997 (79)	1903 (68)	1841 (72)	1786 (74)	1754 (84)	1717 (78)	1707 (79)	1672 (75)
NI-Veh	1991 (57)	1919 (69)	1853 (68)	1831 (70)	1782 (60)	1762 (64)	1718 (54)	1702 (55)
NI-DPC	1925 (47)	1865 (31)	1826 (42)	1767 (44)	1752 (64)	1728 (69)	1699 (67)	1677 (77)
CF (ml g^{-1} min^{-1})								
NI-Cont	83 (4)	79 (4)	77 (4)	76 (4)	76 (4)	75 (4)	73 (3)	72 (3)
NI-Fent	80 (4)	75 (3)	71 (3)	71 (3)	70 (3)	69 (3)	68 (3)	67 (3)
NI-Nal	79 (5)	74 (7)	68 (4)	68 (6)	66 (6)	64 (5)	63 (5)	63 (5)
NI-HD	81 (5)	73 (5)	70 (6)	68 (5)	67 (5)	66 (5)	66 (6)	65 (6)
NI-Veh	78 (3)	71 (4)	69 (3)	67 (3)	66 (3)	65 (2)	65 (2)	65 (2)
NI-DPC	83 (6)	74 (5)	73 (4)	72 (4)	71 (5)	70 (5)	68 (5)	68 (5)

collected and processed using data acquisition and analysis software developed in our department.

PSP and EDP were averaged values computed respectively from 10–14 heart beats. DP was defined as the difference between PSP and EDP. +d*P*/d*t*max and –d*P*/d*t*min were obtained by differentiation of the ventricular pressure signal. These were also averaged values from 10–14 heart beats. EDP was defined as the pressure at the first positive deflection of the left ventricular d*P*/d*t* signal.

Statistical analysis

All values are expressed as mean (SEM). Differences in indices between groups at various times were compared using two-way analysis of variance (ANOVA) for treatment and time with repeated measures on a time factor. If ANOVA indicated significant differences between groups, further comparisons on specific times were performed using Fisher's test. Statistical significance was assumed at $P<0.05$.

Results

Non-ischaemia study

The mechanical indices in the non-ischaemic groups are shown in Table 1. There were no significant differences between groups throughout the study.

Ischaemia study 1

Figures 2 and 3 show changes in DP and –d*P*/d*t*min in groups Cont, Fent, Nal and Fent+Nal. There were no significant differences between groups during the pre-ischaemic period. At the end of reperfusion (60 min), group Fent had a significantly higher DP (58 (3) mm Hg) than all other groups (group Cont 34 (5), group Nal 40 (4) and group Fent+Nal 37 (7) mm Hg) ($P<0.01$). A similar result was obtained for –d*P*/d*t*min, which was also greater in group Fent (943 (34) mm Hg s^{-1}) compared with the other groups (group Cont 578 (83), group Nal 659 (75) and group

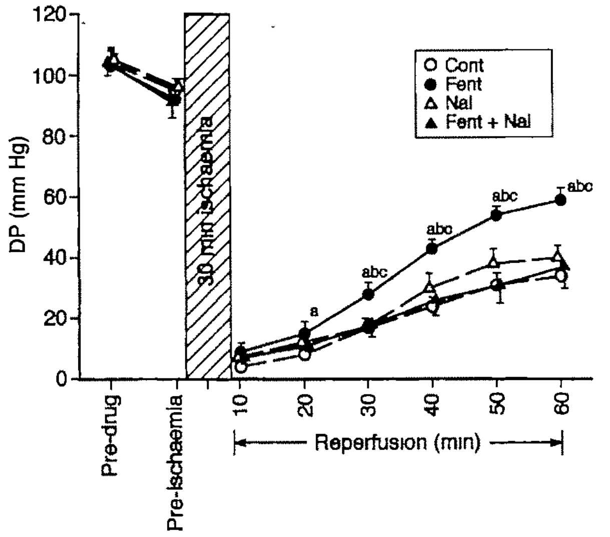


Fig 2 Changes in developed pressure (DP) before and after global ischaemia in groups Cont, Fent, Nal and Fent+Nal (ischaemia study 1). Cont=Control (no drug); Fent=fentanyl, and Nal=naloxone. $^{a}P<0.05$ compared with group Cont, $^{b}P<0.05$ compared with group Nal, $^{c}P<0.05$ compared with group Fent+Nal

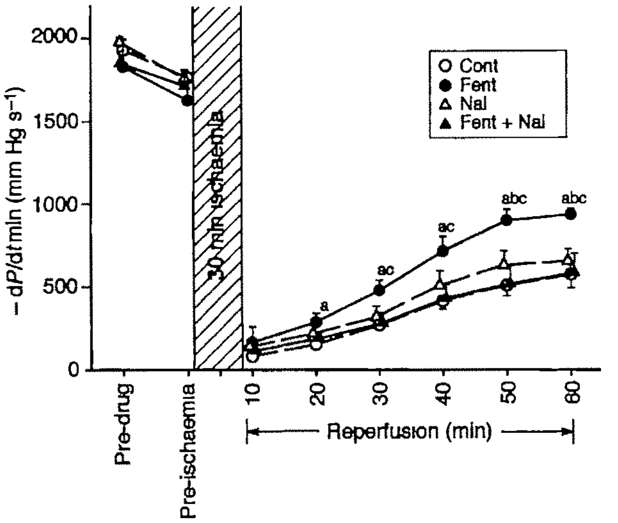


Fig 3 Changes in minimum negative left ventricular pressure derivative (–d*P*/d*t*min) before and after ischaemia in groups Cont, Fent, Nal and Fent+Nal (ischaemia study 1) Cont=Control (no drug), Fent=fentanyl; and Nal=naloxone. $^{a}P<0.05$ compared with group Cont, $^{b}P<0.05$ compared with group Nal, $^{c}P<0.05$ compared with group Fent+Nal

Fent+Nal 588 (117) mm Hg s^{-1}) ($P<0.01$) at 60 min reperfusion. Table 2 shows the changes in the other indices of mechanical function in groups Cont, Fent, Nal and Fent+Nal. +d*P*/d*t*max showed similar recovery to DP and –d*P*/d*t*min. There were no significant differences between groups for EDP or CF.

Figures 4 and 5 and Table 2 show the indices of mechanical function in groups Cont, Fent, HD and Fent+HD. DP (Fig. 4), +d*P*/d*t*max (Table 2) and –d*P*/d*t*min (Fig. 5) showed similar recovery profiles in groups Cont, HD and Fent+HD. There were no significant differences between groups before the ischaemic period. DP ($P<0.05$), +d*P*/d*t*max ($P<0.05$) and –d*P*/d*t*min ($P<0.01$) in group Fent were significantly greater at the end of reperfusion than in all other groups. There were no significant differences in EDP and CF between groups at any time.

Figures 6 and 7 and Table 3 show the changes in indices of mechanical function in groups Veh, Fent+Veh, DPC and Fent+DPC. Groups Veh, DPC and Fent+DPC showed similar recovery profiles for DP (Fig. 6), +d*P*/d*t*max (Table 3) and –d*P*/d*t*min (Fig. 7). DP in group Fent+Veh was significantly greater at the end of reperfusion than in all other groups (group Fent+Veh 59 (5), group Veh 37 (5), group DPC 33 (7) and group Fent+DPC 33 (5) mm Hg) ($P<0.01$). +d*P*/d*t*max and –d*P*/d*t*min were also greater in group Fent+Veh compared with the other groups at the end of reperfusion ($P<0.01$). There was no significant difference in EDP or CF between groups at any time. There were no differences between groups during the pre-ischaemic period.

Ischaemia study 2

No difference was found between groups Fent10 and Fent15 for any index at any time (Table 4). The recovery profiles of DP, +d*P*/d*t*max, –d*P*/d*t*min and EDP in groups Fent10 and Fent15 were similar to those in group Fent.

Discussion

The non-ischaemia study showed that none of the drugs had any effect on the mechanical function of the non-ischaemic heart. It is clear from ischaemia study 1 that fentanyl protected the ischaemic myocardium, enhancing both post-ischaemic systolic (DP and +d*P*/d*t*max) and diastolic (–d*P*/d*t*min) function. Furthermore, ischaemia study 1 suggests that this protection may be blocked by naloxone, 5-HD and DPCPX, as the recovery profiles of mechanical function after ischaemia were similar between groups Nal and Fent+Nal, groups HD and Fent+HD, and groups DPC and Fent+DPC. However, group Fent was not strictly comparable with groups Fent+Nal, Fent+HD and Fent+DPC, because the pre-incubation time of fentanyl was 10 min in groups Fent+Nal, Fent+HD and Fent+DPC and 5 min shorter in group Fent. Therefore, we performed ischaemic study 2 to show that the difference in the pre-incubation time with fentanyl did not cause any difference in the recovery of mechanical function and, therefore, the extent of protection. Our studies demonstrated that the protective effect of fentanyl was blocked by addition of an opioid receptor antagonist, an adenosine A_1 receptor antagonist or the K_{ATP} channel blocker.

While protection against post-ischaemic dysfunction by an opioid has not been reported previously, studies showed that morphine protected against infarction in an *in vivo*[11 12] and an *in vitro* rat model.[13] This effect was blocked by naloxone and a K_{ATP} channel blocker glibenclamide.[11]

Although fentanyl is preferentially a μ opioid receptor

Table 2 Indices of mechanical function before and after global ischaemia in groups Cont, Fent, Nal, Fent+Nal, HD and Fent+HD (ischaemia study 1) DP=Developed pressure, EDP=end-diastolic pressure; +d*P*/d*t*max=maximum positive left ventricular pressure derivative, –d*P*/d*t*min=minimum negative left ventricular pressure derivative; CF=coronary flow Cont=Control (no drug), Fent=fentanyl, Nal=naloxone; and HD=5-HD Results are mean (SEM) $^{a}P<0$ 05 compared with group Cont, $^{b}P<0$ 05 compared with group Nal, $^{c}P<0$ 05 compared with group Fent+Nal, $^{d}P<0$ 05 compared with group HD, $^{e}P<0$ 05 compared with group Fent+HD

			Reperfusion (min)					
	Pre-drug	**Pre-ischaemia**	**10**	**20**	**30**	**40**	**50**	**60**
DP (mm Hg)								
Cont	104 (5)	95 (4)	4 (1)	8 (1)	17 (2)	24 (3)	31 (4)	34 (5)
Fent	103 (5)	92 (3)	9 (3)	15 (4)^{a}	28 (4)^{abc}	43 (3)^{abcde}	54 (3)^{abcde}	59 (4)^{abcde}
Nal	105 (2)	96 (3)	7 (2)	12 (3)	17 (3)	30 (5	38 (5)	40 (4)
Fent+Nal	104 (4)	91 (5)	7 (2)	11 (2)	18 (4)	26 (5)	31 (6)	37 (7)
HD	106 (5)	92 (8)	8 (2)	12 (2)	17 (5)	25 (8)	29 (9)	32 (9)
Fent+HD	109 (5)	94 (6)	9 (5)	14 (6)	18 (6)	25 (6)	31 (7)	36 (7)
EDP (mm Hg)								
Cont	5 (1)	4 (1)	67 (4)	60 (4)	54 (4)	51 (4)	49 (4)	48 (4)
Fent	5 (0)	4 (1)	67 (4)	57 (3)	51 (2)	45 (2)	40 (3)	37 (3)
Nal	4 (0)	4 (1)	64 (5)	56 (4)	51 (3)	43 (5)	39 (5)	37 (5)
Fent+Nal	4 (1)	4 (1)	69 (4)	60 (4)	54 (5)	49 (5)	46 (5)	44 (5)
HD	4 (1)	4 (1)	72 (8)	63 (8)	59 (8)	56 (8)	53 (8)	53 (8)
Fent+HD	4 (1)	4 (1)	64 (7)	56 (6)	52 (6)	49 (6)	46 (6)	43 (6)
+d*P*/d*t*max (mm Hg s^{-1})								
Cont	2764 (180)	2448 (198)	110 (18)	210 (30)	378 (50)	566 (84)	773 (113)	913 (143)
Fent	2666 (152)	2368 (118)	248 (77)^{a}	406 (91)^{a}	709 (143)^{ac}	1127 (130)^{abcde}	1399 (105)^{abcde}	1521 (87)^{abcde}
Nal	2679 (139)	2421 (183)	181 (42)	282 (77)	440 (94)	702 (104)	941 (122)	979 (103)
Fent+Nal	2865 (126)	2552 (103)	142 (21)	258 (54)	406 (84)	635 (129)	819 (168)	944 (184)
HD	2631 (41)	2433 (71)	246 (58)	416 (141)	564 (219)	665 (209)	802 (243)	852 (220)
Fent+HD	2689 (170)	2394 (157)	244 (109)	341 (146)	450 (166)	580 (156)	770 (185)	916 (214)
–d*P*/d*t*min (mm Hg s^{-1})								
Cont	1929 (116)	1767 (135)	83 (13)	153 (16)	273 (26)	415 (49)	510 (66)	578 (83)
Fent	1829 (166)	1629 (117)	167 (52)	289 (61)^{a}	480 (87)^{ac}	719 (68)^{acde}	904 (57)^{abcde}	943 (35)^{abcde}
Nal	1976 (33)	1760 (47)	139 (33)	219 (51)	320 (64)	510 (89)	633 (86)	659 (75)
Fent+Nal	1850 (75)	1716 (98)	117 (12)	191 (34)	286 (57)	433 (87)	521 (107)	588 (117)
HD	1926 (146)	1634 (141)	201 (51)	292 (85)	373 (103)	440 (121)	526 (140)	553 (126)
Fent+HD	2028 (119)	1718 (194)	160 (50)	227 (62)	287 (60)	400 (63)	502 (79)	587 (97)
CF (ml g^{-1} min^{-1})								
Cont	70 (4)	70 (5)	47 (3)	47 (3)	46 (3)	44 (3)	43 (4)	40 (4)
Fent	64 (2)	59 (1)	40 (4)	40 (5)	43 (4)	42 (4)	39 (3)	37 (3)
Nal	72 (5)	67 (5)	52 (6)	52 (6)	51 (7)	48 (7)	45 (8)	44 (8)
Fent+Nal	74 (5)	69 (4)	42 (5)	43 (5)	43 (5)	43 (6)	41 (6)	38 (7)
HD	65 (5)	55 (3)	35 (3)	35 (3)	35 (3)	34 (3)	33 (3)	32 (3)
Fent+HD	60 (6)	52 (5)	39 (4)	39 (4)	39 (3)	36 (4)	33 (3)	32 (3)

agonist, it is capable of binding to δ and κ receptors.[33] Of the several known subtypes of opioid receptor agonists, δ opioid agonists have been shown to provide protection against ischaemic injury. Schultz and colleagues reported that a δ_1 opioid receptor agonist decreased infarct size in an *in vivo* rat model after 30 min of regional ischaemia[34] and that δ, but not μ or κ, opioid antagonists eliminated the protection conferred by morphine in anaesthetized rats.[35] In contrast, κ agonists appeared to enhance cardiac ischaemic injury. Indeed, dynorphin, a κ agonist, decreased ventricular mechanical function *in vivo* in rats,[36] and was arrhythmogenic in both *in vitro*[37] and *in vivo*[38] rat ischaemia models. δ and κ opioid receptors have been characterized in the rat heart,[39 40] but the existence of μ opioid receptors is doubtful. It has been reported that μ opioid receptors are not expressed in the whole heart[39] or in isolated myocytes[40] of rats.

The cellular mechanisms by which fentanyl exerts its post-ischaemic protective action, and the mechanisms whereby an opioid and an adenosine A_1 receptor antagonist block such protective effects are unknown. One hypothesis is based on the PKC model of pharmacologically induced preconditioning. Activation of PKC in the myocyte has been suggested to be the key event in the process of protection.[6 7] Stimulation of PKC-linked receptors by α_1 adrenergic agonists,[41 42] endothelin-1[43 44] and bradykinin[4 45] has been shown to induce protective effects via PKC activation δ-Opioid receptor agonists also enhance PKC activity via G proteins in the myocyte.[8 9] Furthermore, a PKC antagonist has been reported to inhibit morphine-induced preconditioning in the isolated heart preparation.[13] Although involvement of either G proteins or PKC was not examined in our study, PKC activation is a possible explanation for the protective characteristics of fentanyl. In common with α_1 adrenergic, bradykinin and δ opioid receptors, A_1 adenosine receptors have been reported to activate PKC via G proteins in the myocyte.[21] Pretreatment with A_1 adenosine receptor agonists protected the heart against ischaemic injury[17 18 46]

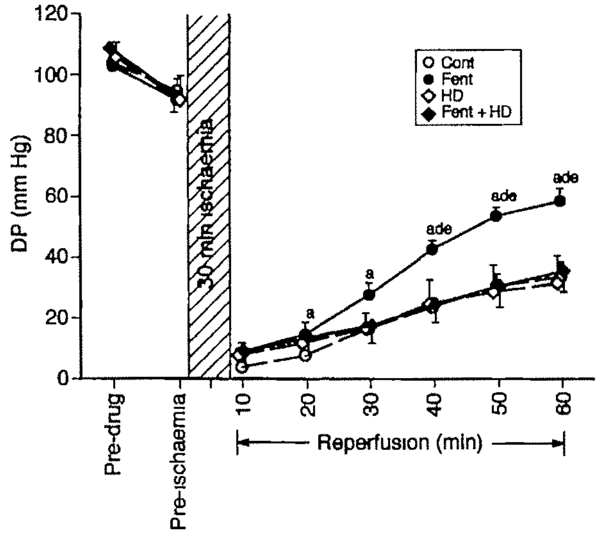


Fig 4 Changes in developed pressure (DP) before and after global ischaemia in groups Cont, Fent, HD and Fent+HD (ischaemia study 1). Cont=Control (no drug), Fent=fentanyl; and HD=5-HD $^{a}P<0.05$ compared with group Cont, $^{d}P<0.05$ compared with group HD, $^{e}P<0.05$ compared with group Fent+HD.

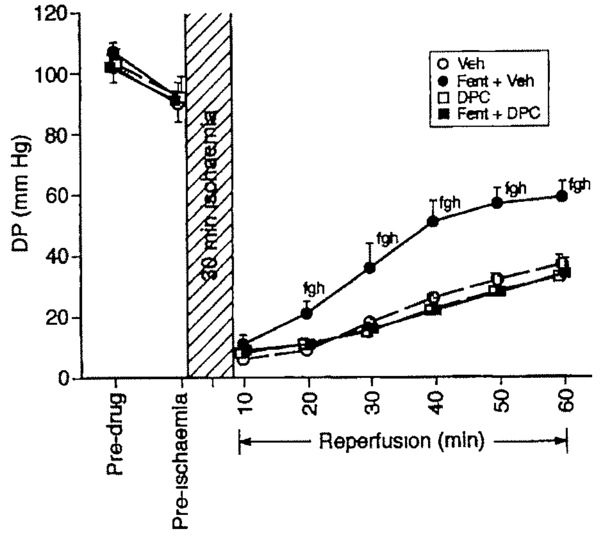


Fig 6 Changes in developed pressure (DP) before and after global ischaemia in groups Veh, Fent+Veh, DPC and Fent+DPC (ischaemia study 1) Veh=Vehicle, Fent=fentanyl; and DPC=DPCPX; $^{f}P<0.05$ compared with group Veh, $^{g}P<0.05$ compared with group DPC, $^{h}P<0.05$ compared with group Fent+DPC.

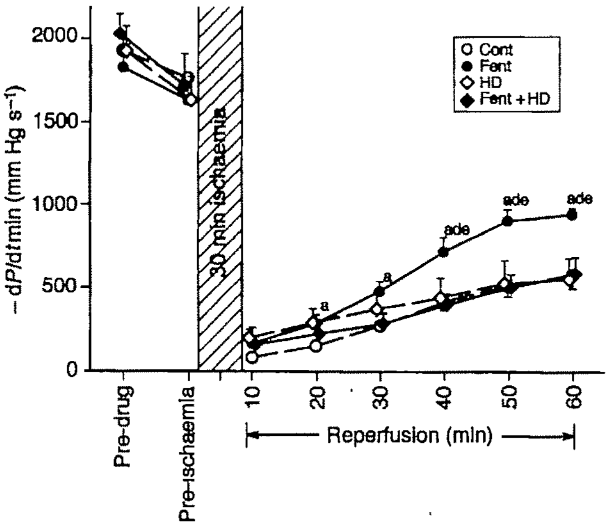


Fig 5 Changes in minimum negative left ventricular pressure derivative (–d*P*/d*t*min) before and after ischaemia in groups Cont, Fent, HD and Fent+HD (ischaemia study 1). Cont=Control (no drug), Fent=fentanyl, and HD=5-HD. $^{a}P<0.05$ compared with group Cont, $^{d}P<0.05$ compared with group HD; $^{e}P<0.05$ compared with group Fent+HD

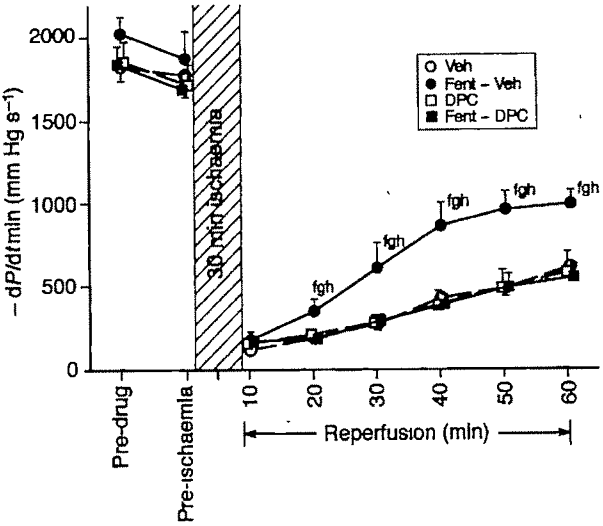


Fig 7 Changes in minimum negative left ventricular pressure derivative (–d*P*/d*t*min) before and after ischaemia in groups Veh, Fent+Veh, DPC and Fent+DPC (ischaemia study 1). Veh=Vehicle; Fent=fentanyl, and DPC=DPCPX. $^{f}P<0.05$ compared with group Veh, $^{g}P<0.05$ compared with group DPC, $^{h}P<0.05$ compared with group Fent+DPC.

and this protection was eliminated by PKC block.[46] Downey and Cohen have suggested that myocardial protection is obtained by the combined activities of several types of receptors, all acting via the PKC pathway.[6] According to their model, protection is achieved only if the activity of PKC exceeds a threshold level. Our results are consistent with such a model, where there were at least two sources for stimulation of PKC: fentanyl acting at the δ opioid receptor which was added to the perfusate, and adenosine released during ischaemia.[16] For protection to occur, the combined effects of these two agonists must increase the activity of PKC above threshold. Hence removing one by addition of either opioid or adenosine A_1 antagonists reduces the activity of PKC below the threshold, abolishing its protective action.

An alternative hypothesis to explain the protection provided fentanyl and the ability of two different types of receptor antagonists to abolish it, is that of an indirect mechanism. For example, the interaction of fentanyl with opioid receptors could result in release of adenosine, which in turn acts on adenosine A_1 receptors to induce a protective effect. There is some evidence for such an indirect action in the spinal cord, where μ and δ opioid receptors have been shown to mediate adenosine release from synapto-

Table 3 Indices of mechanical function before and after global ischaemia in groups Veh, Fent+Veh, DPC and Fent+DPC (ischaemia study 1) DP=Developed pressure, EDP=end-diastolic pressure, +d*P*/d*t*max=maximum positive left ventricular pressure derivative, –d*P*/d*t*min=minimum negative left ventricular pressure derivative, CF=coronary flow Veh=Vehicle, Fent=fentanyl, and DPC=DPCPX Results are mean (SEM) $^{f}P<0.05$ compared with group Veh, $^{g}P<0.05$ compared with group DPC, $^{h}P<0.05$ compared with group Fent+DPC

			Reperfusion (min)					
	Pre-drug	**Pre-ischaemia**	**10**	**20**	**30**	**40**	**50**	**60**
DP (mm Hg)								
Veh	102 (5)	90 (6)	6 (1)	9 (1)	18 (2)	26 (3)	32 (5)	37 (5)
Fent+Veh	107 (3)	92 (5)	11 (3)^{f}	21 (4)^{fgh}	36 (8)^{fgh}	51 (7)^{fgh}	57 (5)^{fgh}	59 (5)^{fgh}
DPC	103 (5)	92 (7)	8 (1)	11 (2)	15 (3)	22 (5)	28 (6)	33 (7)
Fent+DPC	102 (4)	91 (3)	9 (1)	11 (1)	16 (3)	22 (4)	28 (5)	34 (5)
EDP (mm Hg)								
Veh	6 (1)	5 (1)	67 (8)	60 (7)	55 (7)	52 (6)	50 (7)	48 (7)
Fent+Veh	4 (1)	3 (1)	67 (9)	55 (10)	48 (10)	41 (10)	38 (10)	36 (9)
DPC	5 (0)	4 (0)	73 (7)	66 (7)	62 (7)	58 (7)	55 (7)	53 (7)
Fent+DPC	5 (0)	5 (0)	77 (3)	72 (4)	66 (4)	62 (4)	59 (5)	57 (5)
+d*P*/d*t*max (mm Hg s^{-1})								
Veh	2801 (102)	2540 (147)	136 (24)	228 (27)	384 (46)	605 (66)	764 (115)	926 (124)
Fent+Veh	2867 (113)	2608 (188)	279 (66)	521 (104)^{f}	946 (206)^{fgh}	1391 (204)^{fgh}	1589 (175)^{fgh}	1678 (170)^{fgh}
DPC	2679 (139)	2421 (183)	190 (20)	281 (42)	383 (67)	527 (126)	683 (167)	816 (190)
Fent+DPC	2827 (142)	2525 (118)	220 (28)	277 (29)	384 (56)	557 (96)	739 (135)	827 (121)
–d*P*/d*t*min (mm Hg s^{-1})								
Veh	1883 (85)	1771 (129)	120 (25)	192 (16)	272 (37)	430 (37)	490 (48)	614 (58)
Fent+Veh	2020 (101)	1811 (107)	180 (48)	352 (74)^{fgh}	612 (150)^{fgh}	863 (138)^{fgh}	961 (108)^{fgh}	992 (83)^{fgh}
DPC	1850 (122)	1714 (121)	159 (32)	210 (31)	280 (48)	389 (85)	492 (108)	581 (123)
Fent+DPC	1837 (108)	1688 (99)	172 (18)	188 (17)	293 (37)	390 (60)	497 (80)	552 (81)
CF (ml g^{-1} min^{-1})								
Veh	61 (10)	59 (12)	34 (7)	36 (8)	36 (8)	36 (7)	36 (7)	36 (7)
Fent+Veh	64 (5)	57 (5)	43 (5)	44 (5)	43 (5)	42 (6)	42 (5)	42 (5)
DPC	65 (5)	55 (3)	35 (3)	35 (3)	35 (3)	34 (3)	32 (3)	31 (3)
Fent+DPC	60 (6)	52 (5)	39 (4)	39 (4)	39 (3)	36 (4)	33 (3))	32 (3)

Table 4 Indices of mechanical function before and after ischaemia in groups Fent10 and Fent15 (ischaemia study 2). DP=Developed pressure, EDP=end-diastolic pressure, +d*P*/d*t*max=maximum positive left ventricular pressure derivative, –d*P*/d*t*min=minimum negative left ventricular pressure derivative, CF=coronary flow The hearts were perfused with fentanyl in the pre-ischaemic period for 10 min in group Fent10 and for 15 min in group Fent15 No differences between groups

			Reperfusion (min)					
	Pre-drug	**Pre-ischaemia**	**10**	**20**	**30**	**40**	**50**	**60**
DP (mm Hg)								
Fent10	105 (2)	101 (2)	15 (3)	23 (3)	35 (5)	48 (5)	56 (5)	61 (5)
Fent15	108 (3)	103 (3)	13 (3)	22 (3)	36 (4)	51 (5)	57 (6)	61 (4)
EDP (mm Hg)								
Fent10	6 (1)	5 (1)	64 (4)	53 (4)	44 (5)	40 (5)	39 (4)	38 (4)
Fent15	5 (1)	4 (1)	71 (5)	60 (4)	51 (4)	46 (4)	44 (4)	41 (4)
+d*P*/d*t*max (mm Hg s^{-1})								
Fent10	2709 (64)	2573 (54)	328 (53)	540 (88)	836 (120)	1257 (144)	1480 (137)	1612 (144)
Fent15	2796 (88)	2655 (81)	296 (85)	549 (98)	852 (138)	1244 (149)	1433 (147)	1580 (160)
–d*P*/d*t*min (mm Hg s^{-1})								
Fent10	1858 (38)	1757 (46)	247 (60)	370 (58)	562 (67)	748 (82)	926 (107)	996 (103)
Fent15	1860 (94)	1763 (73)	171 (35)	353 (50)	530 (55)	794 (86)	940 (92)	990 (97)
CF (ml g^{-1} min^{-1})								
Fent10	79 (3)	74 (2)	57 (6)	59 (6)	60 (5)	58 (5)	57 (6)	55 (5)
Fent15	72 (4)	71 (4)	55 (4)	57 (3)	57 (3)	57 (3)	56 (2)	55 (2)

somes.[47] By extrapolation from the central nervous system, such release could be thought to occur in the heart. Adenosine release can induce pharmacological preconditioning via PKC, as mentioned above, and may also offer protection via other mechanisms, such as attenuation of production of oxygen-derived free radicals and calcium influx into the myocardium on reperfusion.[19 20] Indeed, in our study, the heart was perfused with fentanyl not only during the pre-ischaemic period but also during reperfusion. Therefore, fentanyl could have exerted its protective effect during reperfusion by a mechanism independent of preconditioning.

There is much speculation that K_{ATP} channels may be the end-effector of myocardial protection. Addition of K_{ATP}

channel openers results in ischaemic preconditioning of the heart.[27–29] Furthermore, the protection produced by PKC-linked receptor agonists, such as adenosine[22] and endothelin-1,[44] is blocked by K_{ATP} channel blockers. Hence it has been proposed that activation of PKC results in the opening of K_{ATP} channels which produce myocardial protection.[32 48 49] There is little evidence of a direct link between opioid receptors and K_{ATP} channels in the myocardium, although the actions of a δ opioid agonist are abolished by a K_{ATP} channel blocker in the vascular[50] and central nervous[51] systems.

In our study, variables of mechanical function were used to examine the extent of ischaemic damage resulting from 30 min of global ischaemia. We cannot determine if improved recovery was caused by more limited irreversible injury (infarction), reduced degree of reversible damage (stunning) or a mixture of both. Isolated rat hearts reperfused after 20 min of total ischaemia have been reported to show no irreversible injuries.[52 53] In contrast, ischaemic periods of longer than 25 min have been shown to result in a mixture of reversible and irreversible histological features.[54] Infarction was found after 30 min of global ischaemia in recent preliminary experiments in our laboratory (unpublished data). Therefore, we assume that the mechanical dysfunction observed in our study reflects both reversible and irreversible myocardial damage. Further studies are needed to determine if fentanyl protects against infarction or stunning.

Regarded as an early diastolic index, $-dP/dt$min represents the speed of relaxation. Adequate supply of ATP is required for the uptake of Ca^{2+} into the sarcoplasmic reticulum so that the myocardium can be relaxed during diastole. It is believed that the supply of ATP is impaired during reperfusion and that this is responsible for the decrease in $-dP/dt$min. EDP indicates compliance of the left ventricle. The increase in EDP is reported to be caused by a combination of intracellular Ca^{2+} overload and other altered myocardial properties, but the detailed mechanism is unknown.[55] In this study, both $-dP/dt$min and EDP were used to evaluate diastolic function. Fentanyl improved $-dP/dt$min significantly but not EDP. The reason for this result remains to be elucidated.

The concentration of fentanyl which exhibited protection in our study was 740 nmol litre^{-1} (250 ng ml^{-1}). The plasma concentration of fentanyl required for anaesthesia in rats is unknown. The clinical plasma concentration of fentanyl in cardiac surgery is 10–30 ng ml^{-1} with a loading dose of 30 μg kg^{-1} followed by a continuous infusion of 0.3 μg kg^{-1} min^{-1}.[56] However, in dogs, a dose of more than 500 ng ml^{-1} was required to obtain anaesthesia when only fentanyl was administered.[57] Pharmacodynamics are largely dependent on species and therefore it is difficult to infer whether or not the concentration used in this study was within the 'therapeutic range'. However, the finding that fentanyl improved post-ischaemic mechanical function was important as fentanyl may offer some cardiac protection in patients with ischaemic heart disease who may suffer from myocardial ischaemia during anaesthesia and surgery.

In summary, the results of our study suggest that fentanyl, an opioid agonist, enhanced the recovery of cardiac mechanical function after ischaemia via an unknown mechanism involving opioid and A_1 adenosine receptors, and K_{ATP} channels. We are currently undertaking further studies to investigate the cellular mechanisms by which fentanyl exerts this protective effect, in particular whether PKC is involved, and whether the protection affects the extent of infarction and/or the degree of stunning. Elucidation of the mechanisms of opioid-mediated protection could pave the way for the development of interventions reducing myocardial ischaemic injury in clinical practice.

Acknowledgements

R. K was in receipt of a Honjo International Scholarship. S. R. was in receipt of a Medical Research Council studentship and a bursary from the Medical Research Fund (University of Oxford). The study was supported in part by a grant from the Garfield Weston Trust for Medical Research into diseases of the heart

References

1 Warltier DC, Al-Wathiqui MH, Kampine JP, Schmelling WT Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**. 552–65

2 Boutros A, Wang J, Capuano C. Isoflurane and halothane increase adenosine triphosphate preservation, but do not provide additive recovery function after ischaemia, in preconditioned rat hearts. *Anesthesiology* 1997; **86**: 109–17

3 Lasley RD, Mentzer RM Jr. Protective effects of adenosine in the reversibly injured heart. *Ann Thorac Surg* 1995; **60**: 843–6

4 Brew EC, Mitchell MB, Rehring TF, *et al.* Role of bradykinin in cardiac functional protection after global ischemia–reperfusion in rat heart. *Am J Physiol* 1995; **269**: H1370–8

5 Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; **74**: 1124–36

6 Downey JM, Cohen MV. Signal transduction in ischemic preconditioning. In: Sideman S, Beyar R. eds. *Analytical and Quantitative Cardiology.* New York: Plenum Press, 1997; 30–55

7 Yellon DM, Baxter GF, Garcia-Dorado D, Heusch G, Sumeray MS. Ischaemic preconditioning: present position and future directions. *Cardiovasc Res* 1998; **37**. 21–33

8 Ela C, Hasin Y, Eilam Y. Opioid effects on contractility, Ca^{2+}-transients and intracellular pH in cultured cardiac myocytes. *J Mol Cell Cardiol* 1993; **25**: 599–613

9 Ela C, Barg J, Vogel Z, Hasin Y, Eilam Y. Distinct components of morphine effects on cardiac myocytes are mediated by the κ and δ opioid receptors. *J Mol Cell Cardiol* 1997; **29**: 711–20

10 Ytrehus K, Bugge E, Starkopf J, Jonassen AK. Mechanism of endogenous protection against infarction in the rat heart. from oxidative stress to signal transduction? *J Mol Cell Cardiol* 1997; **29**. A14

11 Schultz JJ, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. *Circ Res* 1996; **78**: 1100–4

12 Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta (δ)-opioid receptor in the intact rat heart. *J Mol Cell Cardiol* 1997; **29**. 2187–95

13 Miki T, Sato H, Cohen MV, Downey JM. Opioid receptor contributes to ischemic preconditioning through protein kinase C activation in rabbits. *Circulation* 1996; **94** (Suppl. I): I-392–3

14 Schultz JJ, Rose E, Yao Z, Gross GJ. Evidence for involvement of opioid receptors in ischemic preconditioning in rat hearts. *Am J Physiol* 1995; **268**: H2157–61

15 Chien GL, Van Winkle DM Naloxone blockade of myocardial ischemic preconditioning is stereoselective. *J Mol Cell Cardiol* 1996; **28**: 1895–900

16 Mullane K, Bullough D. Harnessing an endogenous cardioprotective mechanisms: Cellular sources and sites of action of adenosine. *J Mol Cell Cardiol* 1995; **27**: 1041–54

17 Thornton JD, Liu GS, Olsson RA, Downey JM Intravenous pretreatment with A_1-adenosine analogue protects the heart against infarction. *Circulation* 1992; **82**: 659–65

18 Downey JM, Liu GS, Thornton JD. Adenosine and the anti-infarct effects of preconditioning. *Cardiovasc Res* 1993, **27**: 3–8

19 Hori M, Kitakaze M. Adenosine, the heart, and coronary circulation. *Hypertension* 1991, **18**. 565–74

20 Forman MB, Velasco CE, Jackson EK. Adenosine attenuates reperfusion injury following regional myocardial ischaemia. *Cardiovasc Res* 1993, **29**: 9–17

21 Henry P, Demolombe S, Puceat M, Escande D. Adenosine A_1 stimulation activated δ-protein kinase C in rat ventricular myocytes. *Circ Res* 1996; **78**: 161–5

22 Auchampach JA, Gross GJ. Adenosine A_1 receptors, K_{ATP} channels, and ischemic preconditioning in dogs. *Am J Physiol* 1993; **264**: H1327–36

23 Neely CF, Dipierro FV, Kong M, Greelish JP, Gardner TJ. A_1 adenosine receptor antagonists block ischemia–reperfusion injury of the heart. *Circulation* 1996, **94** (Suppl. II): II-376–80

24 Thornton JD, Daley JF, Cohen MV, Yang XM, Downey JM. Catecholamines can induce adenosine receptor mediated protection of the myocardium but do not participate in ischemic preconditioning. *Circ Res* 1993; **73**: 649–55

25 Haessler R, Kuzume K, Wolff RA, Chien GL, Davis RF, Van Winkle DM. Adrenergic activation confers cardioprotection mediated by adenosine, but is not required for ischemic preconditioning. *Coron Artery Dis* 1996; **7**: 305–14

26 Kersten JR, Gross GJ, Pagel PS, Warltier DC Activation of adenosine triphosphate-regulated potassium channels. *Anesthesiology* 1998, **88**. 495–513

27 D'Alonzo AJ, Darbenzo RB, Parham CS, Grover GJ Effects of intracoronary cromakalim on postischaemic contractile function and action potential duration: Possible mechanisms of action and ischaemia selectivity. *Cardiovasc Res* 1992; **26**: 1046–53

28 Auchampach JA, Maruyama M, Cavero I, Gross GJ. Pharmacological evidence for a role of ATP-regulated potassium channels in myocardial stunning. *Circulation* 1992; **86**: 311–19

29 Mizumura T, Nithipatikom K, Gross GJ. Bimakalim, an ATP-sensitive potassium channel opener, mimics the effects of ischemic preconditioning to reduce infarct size, adenosine release, and neutrophil function in dogs. *Circulation* 1995; **92**. 1236–45

30 Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC. Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase. *Anesthesiology* 1997; **87**: 361–70

31 Nakayama M, Fujuta S, Tsuchida H, Namiki A. Blockade of ATP-sensitive K^+ channel abolishes the anti-ischemic effects of isoflurane in dog hearts. *Acta Anaesthesiol Scand* 1997, **41**: 531–5

32 Light PE, Sabir AA, Allen BG, Walsh MP, French RJ. Protein kinase C-induced changes in the stoichiometry of ATP binding activate cardiac ATP-sensitive K^+ channels. A possible mechanistic link to ischemic preconditioning *Circ Res* 1996; **79**: 399–406

33 Martin WR. Pharmacology of opioids *Pharmacol Rev* 1983; **35**: 283–323

34 Schultz JJ, Hsu AK, Nagase H, Gross GJ. TAN-67, a δ_1-opioid receptor agonist, reduces infarct size via activation of $G_{i/o}$ proteins and K_{ATP} channels *Am J Physiol* 1998, **274**: H909–14

35 Schultz JJ, Hsu AK, Gross GJ Ischemic preconditioning in the intact rat heart is mediated by δ_1- but not μ- or κ-opioid receptors. *Circulation* 1998, **97**: 1282–9

36 Wu JP, Chen YT, Lee AY. Opioids in myocardial ischaemia: potentiating effects of dynorphin on ischaemic arrhythmia, bradycardia and cardiogenic shock following coronary artery occlusion in the rat. *Eur Heart J* 1993; **14**. 1273–7

37 Wong TM, Lee AY, Tai KK. Effects of drug interacting with opioid receptors during perfusion or ischemia and reperfusion in arrhythmogenesis. *J Mol Cell Cardiol* 1990; **22**. 1167–75

38 Sitsapesan R, Parratt JR. The effects of drugs interacting with opioid receptors on the early ventricular arrhythmias arising from myocardial ischaemia *Br J Pharmacol* 1989; **97**: 795–800

39 Wittert G, Hope P, Pyle D Tissue distribution of opioid receptor gene expression in the rat. *Biochem Biophys Res Commun* 1996, **218**. 877–81

40 Zimlichman R, Gefel D, Eliahou H, *et al.* Expression of opioid receptors during heart ontogeny in normotensive and hypertensive rats *Circulation* 1996; **93**. 1020–5

41 Tsuchida A, Liu Y, Liu GS, Cohen MV, Downey JM α_1-adrenergic agonists precondition rabbit ischemic myocardium independent of adenosine by direct activation of protein kinase C. *Circ Res* 1994; **75**: 576–85

42 Hu K, Nattel S. Mechanisms of ischemic preconditioning in rat heart: Involvement of α_{1B}-adrenoceptors, pertussis toxin-sensitive G proteins, and protein kinase C. *Circulation* 1995; **92**: 2259–65

43 Wang P, Gallagher KP, Downey JM, Cohen MV Pretreatment with endothelin-1 mimics ischemic preconditioning against infarction in isolated rabbit heart. *J Mol Cell Cardiol* 1996, **28**. 579–88

44 Bugge E, Ytrehus K. Endothelin-1 can reduce infarct size through protein kinase C and K_{ATP} channels in the isolated rat heart *Cardiovasc Res* 1996; **35**: 920–9

45 Bugge E, Ytrehus K. Bradykinin protects against infarction but does not mediate ischemic preconditioning in the isolated rat heart *J Mol Cell Cardiol* 1996; **28**: 2333–41

46 Sakamoto J, Miura T, Goto M, Iimura O. Limitation of myocardial infarct size by adenosine A_1 receptor activation is abolished by protein kinase C inhibitors in the rabbit. *Cardiovasc Res* 1995; **29**. 682–8

47 Cahill CM, White TD, Sawynok J Synergy between μ/δ-opioid receptors mediates adenosine release from spinal cord synaptosomes. *Eur J Pharmacol* 1996, **298**: 45–9

48 Liang BT. Protein kinase C-mediated preconditioning of cardiac myocytes: role of adenosine receptor and K_{ATP} channel. *Am J Physiol* 1997; **273**: H847–53

49 Liu Y, Gao WD, O'Rourke B, Marban E. Synergistic modulation of ATP-sensitive K^+ currents by protein kinase C and adenosine Implications for ischemic preconditioning. *Circ Res* 1996, **78**: 443–54

50 Shankar V, Armstead WM. Opioids contribute to hypoxia-induced pial artery dilation through activation of ATP-sensitive K^+ channels. *Am J Physiol* 1995, **269**; H997–1002

51 Ikeda K, Kobayashi T, Ichikawa T, Usui H, Kumanishi T. Functional coupling of the δ- and κ-opioid receptors with the G-protein-activated K^+ channel. *Biochem Biophys Res Commun* 1995, **208**: 302–8

52 Weiss RG, Kalil-Filho R, Hersikowits A, *et al.* Tricarboxyl acid cycle activity in postischemic rat hearts. *Circulation* 1993; **87**: 270–82

53 Yoshida K, Inui M, Harada K, *et al.* Reperfusion of rat heart after brief ischemia induces proteolysis of calspectin (nonerythroid spectrin or fodrin) by calpain. *Circ Res* 1995; **77**: 603–10

54 Moolman JA, Genade S, Winterbach R, Harper IS, Williams K, Lochner A. Preconditioning with a single short episode of global ischemia in the isolated working rat heart: effect on structure, mechanical function, and energy metabolism for various durations of sustained global ischemia. *Cardiovasc Drugs Ther* 1995; **9**· 103–15

55 Opie LH. Ventricular function. In: Opie LH. *The Heart. Physiology, from Cell to Circulation.* Philadelphia: Lippincott-Raven, 1998; 343–89

56 Wynands JE, Wong P, Whally DG, Sprigge JS, Townsent GE, Patel YC. Oxygen–fentanyl anesthesia in patients with poor left ventricular function: Hemodynamics and plasma fentanyl concentrations. *Anesth Analg* 1983, **62**. 476–82

57 Bailey PL, Port JD, McJames S, Reinersman L, Stanley TH. Is fentanyl an anaesthetic in the dog? *Anesth Analg* 1987; **66**: 542–8

British Journal of Anaesthesia **84** (2). 215–20 (2000)

Halothane attenuates the endothelial Ca^{2+} increase and vasorelaxation of vascular smooth muscle in the rat aorta

H. Tsuchida*, S. Seki, S. Tanaka, K. Okazaki and A. Namiki

Department of Anaesthesiology, Sapporo Medical University School of Medicine, Japan
**Corresponding author: Department of Anaesthesiology, Kanazawa Medical University, Daigaku 1–1, Uchinada, Kahoku, Ishikawa 920-0293, Japan*

Isolated spiral strips of rat thoracic aorta with endothelium were suspended for isometric tension recordings in a physiological salt solution. Endothelium-dependent vasorelaxation was elicited by carbachol 10^{-6} and 10^{-5} mol litre^{-1} during norepinephrine-induced contractions, and the effects of 1.5% and 3% halothane were evaluated with concomitant measurement of $[Ca^{2+}]_i$ using fura-2–Ca^{2+} fluorescence. The effects of halothane on endothelium-dependent relaxation were compared with those of nitro^G-L-arginine methyl ester 10^{-4} mol litre^{-1} (L-NAME: an inhibitor of nitric oxide synthase). Carbachol reduced norepinephrine-induced contractions in a concentration-dependent manner, but augmented the norepinephrine-induced increase in $[Ca^{2+}]_i$ in endothelium intact strips. In contrast, carbachol did not influence muscle tension or $[Ca^{2+}]_i$ when the endothelium was completely denuded. Although 3% halothane and L-NAME 10^{-4} mol litre^{-1} inhibited carbachol-induced vasorelaxation in a similar manner, halothane inhibited carbachol-induced increases in $[Ca^{2+}]_i$. These results indicate that halothane inhibited a carbachol-induced increase in $[Ca^{2+}]_i$ in the endothelium, which subsequently attenuated the decrease in muscle tension.

Br J Anaesth 2000; **84**: 215–20

Keywords: anaesthetics volatile, halothane; arteries, aorta; muscle vascular, responses; ions, calcium; rat

Accepted for publication: June 17, 1999

Vascular endothelium produces variable substances, including endothelium-derived relaxing factor (EDRF), prostaglandins, endothelium-derived hyperpolarizing factor (EDHF) and endothelin.[1] EDRF, now proved to be nitric oxide, is produced in vascular endothelium and activates soluble guanylate cyclase in vascular smooth muscle to form 3′,5′-cyclic guanosine monophosphate (cyclic GMP), leading to vasodilatation.[2] Although halothane has been reported to attenuate endothelium-mediated vasodilatation, the mechanisms remain to be elucidated.[3] Several studies have suggested that one of the possible sites of inhibition resides within the endothelium.[4–6]

Increase in the cytosolic concentration of Ca^{2+} ($[Ca^{2+}]_i$) in endothelial cells is an essential step in the synthesis and/or release of nitric oxide.[1 2] Ca^{2+} availability is a likely target of the interaction of halothane with vascular reactivity because it influences Ca^{2+} release from the sarcoplasmic reticulum or Ca^{2+} influx through the sarcolemma in vascular smooth muscle.[7 8] In fact, halothane has been reported to inhibit the bradykinin-induced increase in $[Ca^{2+}]_i$ in cultured bovine aortic endothelial cells[9–11] However, there have been no qualitative studies concerning the effect of halothane on endothelial Ca^{2+} increase and vasorelaxation in a vascular strip

Hence, in this study, we attempted to correlate an increase in endothelial $[Ca^{2+}]_i$ with a decrease in muscle tension, and demonstrate the effect of halothane on this relationship. We measured concomitantly muscle tension and $[Ca^{2+}]_i$ in the vascular smooth muscle of rat thoracic aorta with endothelium using the Ca^{2+} indicator, fura-2 We used carbachol to activate nitric oxide synthase in the endothelium and elicit vasorelaxation. We hypothesized that halothane would interfere with the increase in Ca^{2+} in the endothelium, resulting in reduced vasorelaxation.

Materials and methods

Preparation of muscle strips and measurement of $[Ca^{2+}]_i$

The study was approved by the Animal Care Committee of our institute. The descending thoracic aorta was isolated from male Sprague–Dawley rats (150–200 g) during halothane anaesthesia and cut into spiral strips approximately 10 mm in length and 1 mm in width under a dissecting microscope. The muscle strips were loaded with 5 µmol litre^{-1} of the acetoxymethyl ester of fura-2 (fura-2/AM) solution for 3–5 h at room temperature (23–25°C).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

A non-cytotoxic detergent (0.05% Cremophor EL) was added to solubilize fura-2/AM in a physiological salt solution (PSS). Special care was taken to preserve the endothelium while making spiral strips and during fura-2/AM loading. PSS contained (in mmol litre^{-1}): NaCl 136.9; KCl 5.4; $CaCl_2$ 1.5; $MgCl_2$ 1.0; $NaHCO_3$ 23.8; glucose 5.5; and ethylenediamine tetraacetic acid (EDTA) 0.01. The solution was saturated with a 95% oxygen–5% carbon dioxide mixture at 37°C and pH 7.4.

Experiments were performed with a fluorimeter designed to measure the fluorescence of living tissues (CAF-100; Japan Spectroscopic, Tokyo, Japan), as reported previously.[7 8] The muscle strips were held horizontally in a temperature-controlled organ bath. One end of the muscle strip was connected to a strain gauge transducer (TB-612T; Nihon Kohden, Tokyo, Japan) to monitor mechanical activity. The solution was aerated with 95% oxygen–5% carbon dioxide. A passive tension of 0.5–0.7 g was applied and allowed to equilibrate before the experiment started. From our pilot study, the resting tension allowed us to obtain the maximum contractile response to KCl 32.8 mmol litre^{-1}. The muscle strips were illuminated alternately at 50 Hz at excitation wavelengths of 340±10 nm and 380±10 nm. The amount of 500±20 emitted fluorescence induced by 340 nm excitation (F_{340}) and that induced by 380 nm excitation (F_{380}) were measured successively. We did not calculate the absolute amount of $[Ca^{2+}]_i$ because the calculation could have contained an error of approximately 10% because of endogenous fluorescent substances such as NADH,[12] and also because we do not know the dissociation constant of fura-2 and Ca^{2+} in the cell. Furthermore, the intensity of fura-2–Ca^{2+} fluorescence in the endothelium may be different from that in smooth muscle because of the uneven fura-2 content of these two types of cells.[13] Therefore, the ratio of F_{340} to F_{380} ($R_{340/380}$) was used to indicate changes in $[Ca^{2+}]_i$.

Effect of halothane on endothelium-dependent vasodilatation

After an equilibration period (20–30 min), isometric muscle contraction was induced with norepinephrine 10^{-8} mol litre^{-1} This concentration evoked approximately 60% of the maximal norepinephrine-induced contraction in our pilot study. Increases in muscle tension and $R_{340/380}$, 5 min after administration of norepinephrine were regarded as reference values (100%). The muscle strips were then challenged with carbachol 10^{-6} and 10^{-5} mol litre^{-1} to elicit vasorelaxation. Changes in muscle tension and $R_{340/380}$ were expressed as percentages of reference values. This procedure was repeated three times in a control muscle strip to verify the presence of endothelium throughout the experiment. In the halothane groups, we used the same experimental set-up as in the control strip except for the second set of contractions, in which either 1.5% or 3% halothane was administered through the oxygen–carbon dioxide mixture from 8 min before to the end of contraction ($n=6$ animals). In other muscle strips ($n=6$), the second set of contractions was performed in the presence of nitro^G-L-arginine methyl ester 10^{-4} mol litre^{-1} (L-NAME, an inhibitor of nitric oxide synthase) to compare the effect of halothane on endothelium-dependent vasorelaxation.

Carbachol-induced changes in muscle tension and $[Ca^{2+}]_i$ were also determined in muscle strips from which the endothelium had been denuded either completely with a cotton swab moistened with PSS ($n=6$), or only in a small area using a stainless steel rod where fura-2–Ca^{2+} fluorescence was detected ($n=6$) (Fig. 1A). Nitroglycerine, an endothelium-independent relaxant, was also used as a nitric oxide donor to activate guanylyl cyclase and induce vasorelaxation in the muscle strips without endothelium ($n=6$). In these experiments, changes in Ca^{2+} in smooth muscle only were detected.

Drugs

The following drugs and chemicals were used: fura-2/AM (Dojindo Laboratories, Kumamoto, Japan), Cremophor EL, norepinephrine, carbachol, nitro^G-L-arginine methyl ester (Sigma Chemical Co., St Louis, USA) and halothane (Takeda Pharmaceuticals, Tokyo, Japan). Nitroglycerine was kindly donated by Nippon Kayaku Pharmaceuticals (Tokyo, Japan). The concentration of halothane in the gas mixture was monitored continuously using a precalibrated anaesthetic agent monitor (Model 303; Atom, Tokyo, Japan). The concentration of halothane in the bath fluid was determined by testing 2-µl aliquots of PSS using gas chromatography (GC-17A; Shimadzu, Tokyo, Japan). Concentrations were 0.44±0.02 mmol litre^{-1} and 0.87±0.03 mmol litre^{-1} for 1.5% and 3% halothane, respectively. These are equivalent to 1.47% and 2.9% halothane.

Statistical methods

Data are expressed as mean (SD). Statistical evaluation was performed using the Student's *t* test or analysis of variance (ANOVA) for multiple comparisons. $P<0.05$ was considered significant. When significant variance ratios were obtained using ANOVA, a *post hoc* analysis was performed using Fisher's protected least significant difference test.

Results

We produced 6–8 endothelium intact strips from each rat thoracic aorta. However, not all strips responded to carbachol sufficiently after fura-2 loading, probably because of endothelial damage. Therefore, we considered endothelium intact muscle strips as those that reduced norepinephrine-induced contractions by more than 80% after exposure to carbachol 10^{-5} mol litre^{-1}. Usually, two or three strips were discarded as the response to carbachol was insufficient.

In control experiments, norepinephrine simultaneously increased muscle tension and $R_{340/380}$ (Fig. 1B, Table 1). Carbachol, administered during norepinephrine-induced contraction, elicited concentration-dependent augmentation

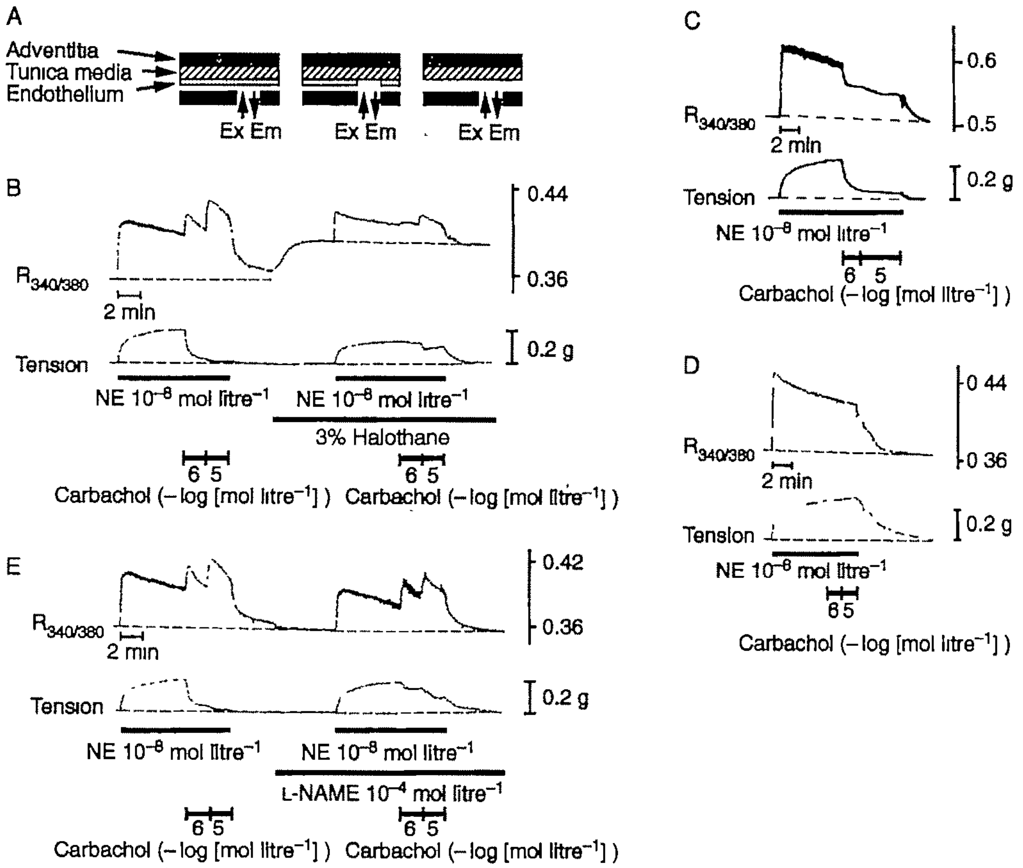


Fig 1 A Schematic illustration of the method for measuring $[Ca^{2+}]_i$ in endothelium or smooth muscle, or both, in the aorta loaded with fura-2 Left intact endothelium, middle: endothelium removed from a small area where fura-2–Ca^{2+} fluorescence was detected; right: endothelium completely removed. Ex=Excitation; Em=emission B: Typical recordings of the effect of carbachol on norepinephrine (NE)-induced increases in $[Ca^{2+}]_i$ (indicated as $R_{340/380}$) and muscle tension in the strips with endothelium. Left norepinephrine evoked an increase in muscle tension and $[Ca^{2+}]_i$ simultaneously in the control state; right· 3% halothane significantly attenuated both a carbachol-induced decrease in muscle tension and an increase in $[Ca^{2+}]i$ C Recordings of strips from which the endothelium was removed in a small area where fura-2–Ca^{2+} fluorescence was detected D Recordings of strips without endothelium E Effects of nitro^G-L-arginine (L-NAME) on carbachol-induced vasorelaxation and $[Ca^{2+}]_i$ increase

Table 1 Norepinephrine-induced increases in muscle tension in the three sets of contractions (mean (SD)) In the control group, the three sets of contractions were comparable In the 1 5% and 3% halothane groups, however, the second set of contractions was significantly reduced compared with the first and third sets. The third set of contractions was not determined (nd) in the nitro^G-L-arginine (L-NAME) group because the effect of L-NAME was not reversed by washing out or by administration of L-arginine 10^{-4} mol litre^{-1}

	1st contraction (g)	2nd contraction (g)	3rd contraction (g)	P
Control	0.29 (0.02)	0.29 (0.02)	0.29 (0.02)	0.793
Halothane 1.5%	0.30 (0.02)	0.24 (0.01)	0.29 (0.02)	<0.0001
Halothane 3%	0.26 (0.04)	0.17 (0.02)	0.26 (0.05)	<0.0001
L-NAME	0.24 (0.04)	0.23 (0.03)	nd	0.201

of the increase in $R_{340/380}$ which was accompanied by a concentration-dependent decrease in muscle tension. Carbachol 10^{-6} mol litre^{-1} caused a decrease in muscle tension of 82 (2)%, whereas there was an increase in $R_{340/380}$ of 59 (35)%. In contrast with endothelium intact strips, carbachol reduced the increases in both muscle tension and $R_{340/380}$ in muscle strips in which the endothelium had been partially removed from an area where fura-2–Ca^{2+} fluorescence was detected (Fig. 1C). Carbachol did not affect muscle tension or $R_{340/380}$ when the endothelium was completely denuded (Fig. 1D). Nitroglycerine 10^{-6} mol litre^{-1} decreased norepinephrine-induced increases in muscle tension and $R_{340/380}$ by 85 (3)% and 49 (11)%, respectively.

In control experiments, carbachol-induced decreases in muscle tension and increases in $R_{340/380}$ were comparable among the three sets of contractions (Fig. 2A). Therefore, we compared the first two sets in subsequent experiments. Halothane, administered in the resting state, significantly increased $R_{340/380}$ with little change in muscle tension (Fig. 1B). In the presence of halothane, norepinephrine caused muscle contraction and an increase in $R_{340/380}$. However, increases in muscle tension were significantly attenuated by halothane in a concentration-dependent manner (Table 1). Halothane also reduced carbachol-induced vasorelaxation in a concentration-dependent manner (Figs 2, 3). In contrast, the effect of halothane on the increase in $R_{340/380}$ was not significant, probably because we measured fluorescence not only from the endothelium but also from smooth muscle (Fig. 3). To assess the effect of halothane on endothelial $[Ca^{2+}]i$, we used L-NAME to produce similar vasorelaxation

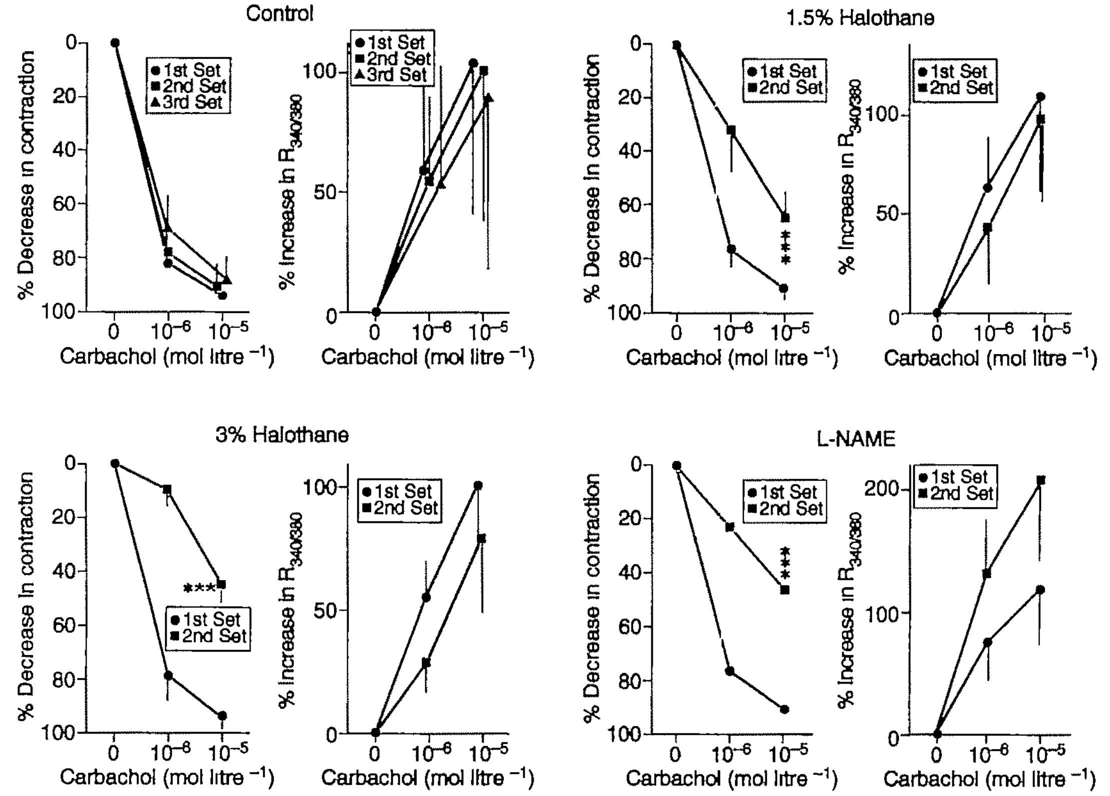


Fig 2 Effects of halothane and nitro^G-L-arginine (L-NAME) on the carbachol-induced decrease in muscle tension and increase in $R_{340/380}$ in strips preconstricted with norepinephrine 10^{-8} mol litre^{-1} Data are mean (SD) Halothane or L-NAME was administered during the second set of contractions. ***$P<0.001$ *vs* first set of contractions

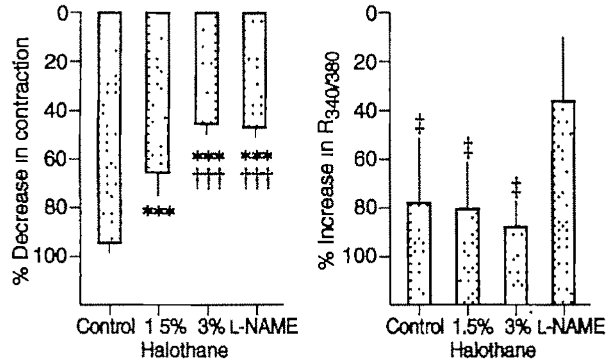


Fig 3 Comparison of carbachol-induced (10^{-5} mol litre^{-1}) decreases in muscle tension (left) and increases in $R_{340/380}$ (right) in the second set of contractions in each experiment. Both concentrations of halothane and nitro^G-L-arginine (L-NAME) significantly reduced carbachol-induced vasorelaxation. However, only L-NAME augmented the carbachol-induced increase in $R_{340/380}$ Data are mean (SD). ***$P<0.001$ *vs* control, †††$P<0.001$ *vs* 1.5% halothane, ‡$P<0.05$ *vs* L-NAME.

as observed during 3% halothane. Although there was no significant difference in muscle tension between 3% halothane and L-NAME 10^{-4} mol litre^{-1} during application of carbachol 10^{-5} mol litre^{-1}, the increase in $R_{340/380}$ was significantly greater in the L-NAME group than in the 3% halothane group (Figs 1E, 3).

Discussion

We have demonstrated that: (1) in strips without endothelium, carbachol did not influence vascular reactivity, but nitroglycerine reduced both norepinephrine-induced increases in muscle tension and $[Ca^{2+}]_i$; (2) carbachol reduced muscle tension and an increase in $[Ca^{2+}]_i$ in strips from which the endothelium had been partially denuded at the area where fura-2–Ca^{2+} fluorescence was detected; (3) in strips with endothelium, carbachol reduced muscle contraction but augmented the norepinephrine-induced increase in $[Ca^{2+}]$i, halothane altered carbachol-induced changes in both Ca^{2+} mobilization and vasorelaxation, and L-NAME affected carbachol-induced vasorelaxation but enhanced the increase in $[Ca^{2+}]_i$.

The vasorelaxing effects of carbachol depend on the endothelium in the rat thoracic aorta. This was clearly shown in our experiments. Carbachol did not influence vascular reactivity in strips without endothelium. When the endothelium was functioning, however, carbachol lowered $[Ca^{2+}]_i$ and muscle tension, as observed in the partially denuded endothelium strips. Muscarinic agonists such as carbachol produce not only nitric oxide but EDHF in the endothelium, leading to endothelium-induced vasorelaxation.[14] L-NAME inhibits the production of nitric oxide from L-arginine, but does not affect the production of

EDHF. Therefore, L-NAME 10^{-4} mol litre^{-1} could not completely antagonize the effect of carbachol on endothelium-dependent vasorelaxation in our study.

Production of nitric oxide or other vasorelaxing substances requires an increase in $[Ca^{2+}]_i$ in the endothelium;[1] this was shown in the endothelium intact strips where carbachol increased $[Ca^{2+}]_i$ and reduced muscle tension in a concentration-dependent manner. In the strips with endothelium, fura-2–Ca^{2+} fluorescence was obtained from both the endothelium and smooth muscle. As a result, the carbachol-induced change in $R_{340/380}$ consisted of two components: a change in $[Ca^{2+}]_i$ in the endothelium and a concomitant change in $[Ca^{2+}]_i$ in smooth muscle. When nitroglycerine 10^{-6} mol litre^{-1} was used as a nitric oxide donor, the drug decreased norepinephrine-induced contractions in a manner comparable with that of carbachol 10^{-6} mmol litre^{-1}. This nitroglycerine-induced decrease in muscle tension was accompanied by a concomitant decrease in $[Ca^{2+}]_i$ in smooth muscle. These results strongly suggest that carbachol increased $[Ca^{2+}]_i$ in the endothelium but decreased $[Ca^{2+}]_i$ in smooth muscle. Therefore, carbachol-induced increases in $R_{340/380}$ most likely produced underestimation of the real increases in $[Ca^{2+}]_i$ in the endothelium. The more the endothelium produces vasorelaxing substances, the greater is the reduction in muscle tension and $[Ca^{2+}]_i$ in smooth muscle.[13 15]

Halothane 3% and L-NAME 10^{-4} mmol litre^{-1} inhibited endothelium-mediated vasorelaxation in a similar manner. As a result, a similar reduction in $[Ca^{2+}]_i$ in smooth muscle was anticipated during administration of 3% halothane and L-NAME 10^{-4} mol litre^{-1} in response to carbachol. Therefore, the different response of $R_{340/380}$ to carbachol during the two experiments can be attributed to the endothelium. L-NAME does not influence Ca^{2+} entry into endothelial cells and therefore does not cause an increase in $[Ca^{2+}]_i$.[16] The increased response of $R_{340/380}$ to carbachol during L-NAME should have reflected a smaller reduction in $[Ca^{2+}]_i$ in smooth muscle rather than a greater increase in $[Ca^{2+}]_i$ in the endothelium. In contrast, the carbachol-induced increase in $R_{340/380}$ during 3% halothane was lower than that during L-NAME. These results indicate that 3% halothane attenuated not only vasorelaxation but also the $[Ca^{2+}]_i$ response to carbachol. This observation is consistent with previous reports indicating that halothane-induced suppression of Ca^{2+} mobilization is involved in the mechanisms of halothane-induced inhibition of endothelium-mediated vasorelaxation.[9–11]

We did not identify the mechanism of halothane modulation of Ca^{2+} mobilization in the endothelium. In addition, suppression of endothelial Ca^{2+} mobilization by halothane is unlikely to be the sole factor contributing to halothane-induced inhibition of endothelium-mediated vasodilatation because halothane reduces endothelium-dependent vasodilatation induced not only by receptor agonists to the endothelium but also by the Ca^{2+} ionophore A23187.[17] Further study is needed to define the underlying mechanisms.

In summary, we have provided strong evidence that suppression of Ca^{2+} mobilization in the endothelium is involved in the inhibitory effect of halothane on endothelium-dependent vasorelaxation.

Acknowledgement

We are grateful to Paul A Murray, PhD, Director, Center for Anesthesiology Research, Cleveland Clinic Foundation, for reviewing the manuscript.

References

1 Graier WF, Sturek M, Kukovetz WR Ca^{2+} regulation and endothelial vascular function. *Endothelium* 1994, **1**. 223–6

2 Moncada S, Palmer RMJ, Higgs EA. Nitric oxide, physiology, pathology, and pharmacology *Pharmacol Rev* 1991, **43** 109–42

3 Johns RA. Endothelium, anesthetics, and vascular control. *Anesthesiology* 1993; **79**: 1381–91

4 Hart JL, Jing M, Bina S, Freas W, Van Dyke RA, Muldoon SM. Effects of halothane on EDRF/cGMP-mediated vascular smooth muscle relaxations. *Anesthesiology* 1993; **79**. 323–31

5 Blaise G, To Q, Parent M, Lagarde B, Asenjo F, Sauve R. Does halothane interfere with the release, action, or stability of endothelium-derived relaxing factor/nitric oxide? *Anesthesiology* 1994; **80**: 417–26

6 Johns RA, Tichotsky A, Muro M, Spaeth JP, Le Cras TD, Rengasamy A. Halothane and isoflurane inhibit endothelium-derived relaxing factor-dependent cyclic guanosine monophosphate accumulation in endothelial cell–vascular smooth muscle co-cultures independent of an effect on guanylyl cyclase activation. *Anesthesiology* 1995; **83**: 823–34

7 Tsuchida H, Namba H, Yamakage M, Fujita S, Notsuki E, Namiki A. Effects of halothane and isoflurane on cytosolic calcium ion concentrations and contraction in the vascular smooth muscle of the rat aorta. *Anesthesiology* 1993; **78**. 531–40

8 Tsuchida H, Namba H, Seki S, Fujita S, Tanaka S, Namiki A. Role of intracellular Ca^{2+} pools in the effects of halothane and isoflurane on vascular smooth muscle contraction *Anesth Analg* 1994; **78**: 1067–76

9 Loeb AL, Longnecker DE, Williamson JR. Alteration of calcium mobilization in endothelial cells by volatile anesthetics *Biochem Pharmacol* 1993, **45**. 1137–42

10 Simoneau C, Thuringer D, Cai S, Garneau L, Blaise G, Sauve R Effects of halothane and isoflurane on bradykinin-evoked Ca^{2+} influx in bovine aortic endothelial cells *Anesthesiology* 1996; **85**: 366–79

11 Pajewski TN, Miao N, Lynch C III, Johns RA Volatile anesthetics affect calcium mobilization in bovine endothelial cells. *Anesthesiology* 1996, **85** 1147–56

12 Ozaki H, Sato K, Satoh T, Karaki H. Simultaneous recordings of calcium signals and mechanical activity using fluorescent dye fura-2 in isolated strips of vascular smooth muscle *Jpn J Pharmacol* 1987; **45**: 429–33

13 Sato K, Ozaki H, Karaki H. Differential effects of carbachol on cytosolic calcium levels in vascular endothelium and smooth muscle *J Pharmacol Exp Ther* 1990; **255**: 114–19

14 Taylor SG, Weston AH Endothelium-derived hyperpolarizing factor. a new endogenous inhibitor from the vascular endothelium *Trends Pharmacol Sci* 1988, **9**: 272–4

15 Amano K, Hori M, Ozaki H, Karaki H. Agonist-dependent difference in the relationship between cytosolic Ca^{2+} level and

release of vascular relaxing factors in the endothelium of rabbit aortic valve. *Eur J Pharmacol* 1999; **366**: 215–21

16 Sudjarwo SA, Hori M, Karaki H. Effect of endothelin-3 on cytosolic calcium level in vascular endothelium and on smooth muscle contraction. *Eur J Pharmacol* 1992; **229**: 137–42

17 Uggeri MJ, Proctor GJ, Johns RA. Halothane, enflurane, and isoflurane attenuate both receptor- and non-receptor-mediated EDRF production in rat thoracic aorta. *Anesthesiology* 1992; **76**: 1012–17

British Journal of Anaesthesia 84 (2). 221–5 (2000)

Effects of xenon on cerebral blood flow and autoregulation: an experimental study in pigs

H. Fink*, M. Blobner, R. Bogdanski, F. Hänel, C. Werner and E. Kochs

Klinic für Anaesthesiologie der Technischen Universität München, Klinikum rechts der Isar,
Ismaninger Str. 22, 81675 Munich, Germany

**Corresponding author*

We have investigated the effects of xenon on regional cerebral blood flow (rCBF) and autoregulation in pigs sedated with propofol 4 mg kg^{-1} h^{-1}. Balloon-tipped catheters were placed into the descending aorta and inferior vena cava of 15 Gottingen Minipigs for manipulation of arterial pressure and blood sampling. rCBF was measured using the sagittal sinus outflow technique. Xenon was adjusted randomly to end-tidal fractions (FE'_{Xe}) of 0, 0.30, 0.50 and 0.70. After baseline measurements of heart rate (HR), mean arterial pressure (MAP), rCBF, sagittal sinus pressure (SSP) and calculation of regional cerebrovascular resistance (rCVR) at each respective FE'_{Xe}, autoregulation was tested in the MAP range 60–120 mm Hg. Increasing FE'_{Xe} had no effect on HR, MAP, rCBF or SSP. rCVR increased with increases in MAP, regardless of FE'_{Xe}. Autoregulation was not impaired. We conclude that xenon inhalation had no effect on rCBF and autoregulation in our model, which could suggest that xenon is an adequate adjunct for neurosurgical anaesthesia.

Br J Anaesth 2000; **84**: 221–5

Keywords: anaesthetics gases, xenon; brain, blood flow; brain, autoregulation; pig

Accepted for publication: September 20, 1999

The noble gas xenon is an inhalation anaesthetic agent with physicochemical characteristics that provide rapid induction[1] and emergence from anaesthesia[2 3] while maintaining haemodynamic and neurohumoral stability.[4–7] At end-tidal fractions of 0.70, xenon provides better analgesia than nitrous oxide.[5] While nitrous oxide increases cerebral blood flow (CBF),[8] it is unclear if xenon has similar cerebrovascular effects.

Xenon (stable or radiolabelled) has also been used as an inert tracer for measurement of CBF. However, studies in laboratory animals and humans suggest that inhalation of xenon modulates cerebrovascular tone which could make this compound an unfavourable alternative to radioactive tracers.[9–13] It is possible that the cerebrovascular effects of xenon in these studies were related to unstable experimental preparations or poorly controlled physiological variables.[10–12 14 15] In this study, we have investigated the steady state effects of xenon inhalation on CBF and cerebral autoregulation in pigs sedated with propofol.

Materials and methods

Animal model

After approval of the Animal Use and Care Committee (AZ 211-2531 –62/97 Regierung von Oberbayern), we studied 15 microbiologically controlled female Göttingen Minipigs weighing 25–35 kg (Ellegaard Göttingen Minipigs ApS, Dalmose, Denmark). After administration of ketamine 15 mg kg^{-1} i.m., azaperone 2 mg kg^{-1} i.m and atropine 0.5 mg i.m., anaesthesia was induced with propofol 1–1.5 mg kg^{-1} i.v. and the trachea intubated. Ventilation was set to maintain an end-tidal carbon dioxide partial pressure of 4.7 kPa (FI_{O_2} 0.3) (Elvira, GambroEngstrøm, Broma, Sweden). Anaesthesia was maintained by continuous infusion of ketamine 4 mg kg^{-1} h^{-1} and propofol 4 mg kg^{-1} h^{-1}.

Heart rate was measured using adhesive ECG electrodes A Shaldon catheter (9-French gauge) was inserted into the external jugular vein. An introducer sheath was placed in the right femoral artery and a pulmonary artery catheter was inserted for continuous measurement (Sirecust 404–1, Siemens, Erlangen, Germany) of mean arterial pressure (MAP) and arterial blood sampling. Via an introducer sheath in the femoral vein, a Fogarty catheter (5-French gauge) was placed into the inferior vena cava. On the day of the study, both balloon catheters were brought into the correct position (i.e. proximal enough to induce haemodynamic changes) and controlled by x-ray. This enabled manipulations of arterial pressure by either inflation of the arterial balloon and consequently causing an increase in cardiac afterload with elevation of MAP or by inflation of the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

caval balloon resulting in a decrease in cardiac preload (caval block) and MAP reduction. Core body temperature, measured at the tip of the aortic catheter, was maintained at 36.5–37.5°C using heating pads.

Regional cerebral blood flow (rCBF) of the frontal hemispheres was measured using the sagittal sinus outflow technique. For this purpose, the skull cap was removed over the entire convexity. The septa of the underlying frontal sinuses were resected and the lining mucosa removed. The remaining bone covering the brain was deprived from its circulation by abrading the outer cortical layer and the spongiosa using a drill with saline irrigation. A thin bone lamella was left to cover the brain. Any bleeding from the bone was coagulated and sealed with bone wax to minimize extracranial blood flow into the superior sagittal sinus. For cannulation of the superior sagittal sinus, the bone lamella was removed carefully over a large area of 20×2 mm directly above the sinus, which was then cannulated using a 16-gauge cannula. A balloon-tipped catheter (4-French gauge) was inserted distal to the outflow catheter into the caudal segment of the sagittal sinus to ensure complete drainage of the sinus and to measure sagittal sinus pressure (SSP). After the surgical preparation was completed, all catheters were locked with heparinized saline. I.v. sedation was maintained with propofol 4 mg kg^{-1} h^{-1} and the animals were allowed to equilibrate for a period of 18 h. This sedation regimen ensured that all pigs were able to cough during tracheal suction or to move in response to pain stimuli. Using repeated arterial blood-gas analyses, physiological variables were controlled.

One hour before starting the measurements, neuromuscular block was produced with a bolus dose of cis-atracurium 0.3 mg kg^{-1} followed by infusion of 2 mg kg^{-1} h^{-1} while propofol sedation remained unchanged. The pigs were placed in the prone position and given a bolus dose of heparin 10 000 u. i.v. followed by infusion of 2500 u. h^{-1}. The locked catheters were flushed. The sagittal sinus catheter was connected to the Shaldon catheter (9-French gauge) placed in the external jugular vein, creating a shunt between the superior sagittal sinus and the external jugular vein. An integrated ultrasound flow probe (Transonic In-Line Flow Probe 2N758, Transonic Systems Inc., Ithaca, NY, USA) enabled continuous measurement of sagittal sinus blood flow (Transonic Systems Inc., T206, Transonic Systems Inc., Ithaca, NY, USA). The balloon-tipped catheter (4-French gauge) was inflated in the caudal segment of the sinus to the extent of maximum outflow values.

Measurements

The ability of our preparation to measure changes in CBF was confirmed by testing the carbon dioxide reactivity of the cerebral vessels before the measurements. This manoeuvre was repeated after completing all measurements to ensure intact reactivity throughout the experiments. End-tidal xenon fractions ($F\text{E}'_{\text{Xe}}$) of 0, 0.30, 0.50 and 0.70 were applied in random order by inhalation, using a Cicero respirator adapted for administration of xenon (Dräger, Lübeck, Germany). $F\text{E}'_{\text{Xe}}$ was measured continuously using a gas chromatograph (Xenotec, Dräger, Lübeck, Germany). After 30 min of stable $F\text{E}'_{\text{Xe}}$ at each respective level, baseline measurements of HR, MAP, rCBF and SSP were performed to evaluate the effect of xenon alone. Cerebral perfusion pressure (CPP) was calculated by: CPP=MAP−SSP (mm Hg).

After each baseline measurement, autoregulation was tested at the same $F\text{E}'_{\text{Xe}}$ by randomly adjusting four target MAP levels at approximately 60, 80, 100 and 120 mm Hg for at least 5 min. At each target level, arterial blood-gas analysis was performed and carbon dioxide partial pressures exceeding 4.7–5.2 kPa were corrected by adjusting ventilation. Subsequently, MAP, rCBF and SSP were documented. Regional cerebrovascular resistance (rCVR) was calculated as: $\text{rCVR}=\text{CPP}\times\text{rCBF}^{-1}$ (mm Hg min ml^{-1}).

On completion of the measurements, the animals were killed by injection of potassium. Ink was injected in a retrograde manner into the sagittal sinus to stain the brain regions drained by the shunt. The stained areas were carefully resected and weighed. Sinus outflow was then calculated per 100 g of brain tissue.

Data analysis and statistical evaluation

Data on the effects of xenon alone were compared using repeated measures analysis of variance. Data on autoregulation (rCBF, SSP, and rCVR) by balloon manipulations were tested by multiple linear regression analyses with the variables MAP, $F\text{E}'_{\text{Xe}}$ and their interaction ($\text{MAP}\times F\text{E}'_{\text{Xe}}$).

The autoregulation coefficient was defined as the slope of the linear regression of the MAP/rCBF relationship and was calculated for each xenon concentration and each individual pig. By definition, a horizontal line (slope=0) indicates intact autoregulation. Autoregulation was considered intact when the increase in rCBF within the given MAP range was less than 0.15 ml 100 g $brain^{-1}$ min^{-1} mm Hg^{-1}. The choice of the statistical tests was based on data from a preliminary study in five pigs. In these animals, the SD of the MAP/rCBF relationship was 0.058 ml 100 g $brain^{-1}$ min^{-1} mm Hg^{-1} during propofol anaesthesia. The critical difference was set to half of the acceptable increase in the slope from 0 to 0.15 ml 100 g $brain^{-1}$ min^{-1} mm Hg^{-1} which may be induced by xenon. Power analysis ($\alpha=0.01$; $\beta=0.20$) indicated 11 animals were needed to reject the null hypothesis (slope >0.15). An α level of 0.01 was chosen to account for the four repeated measurement design of the study. Student's *t* tests were performed at each xenon level.

Carbon dioxide reactivity, approximately 30 min before starting the study, was compared with values obtained 1 h after exhalation of xenon to verify the stability of the model over time using paired *t* tests ($P<0.1$).

Results

End-tidal xenon fractions did not affect baseline values of HR, MAP, rCBF, SSP or CPP (Table1). Figure 1 shows

Table 1 Heart rate (HR), mean arterial pressure (MAP), regional cerebral blood flow (rCBF), sagittal sinus pressure (SSP) and cerebral perfusion pressure (CPP) at baseline with end-tidal fractions of xenon $F\text{E}'_{\text{Xe}}$ of 0, 0.30, 0.50 and 0.70 (mean (SD))

	$F\text{E}'_{\text{Xe}}$ 0	$F\text{E}'_{\text{Xe}}$ 0.30	$F\text{E}'_{\text{Xe}}$ 0.50	$F\text{E}'_{\text{Xe}}$ 0.70
HR (beat min^{-1})	103 (21)	104 (20)	101 (11)	105 (14)
MAP (mm Hg)	100 (14)	92 (11)	90 (17)	94 (19)
rCBF (ml 100 g^{-1} min^{-1})	37.9 (11.6)	37.4 (9.6)	38.9 (11.1)	39.3 (9.0)
SSP (mm Hg)	5.4 (3.0)	5.7 (2.8)	5.9 (3.3)	5.9 (3.1)
CPP (mm Hg)	95 (13)	86 (12)	84 (19)	88 (20)

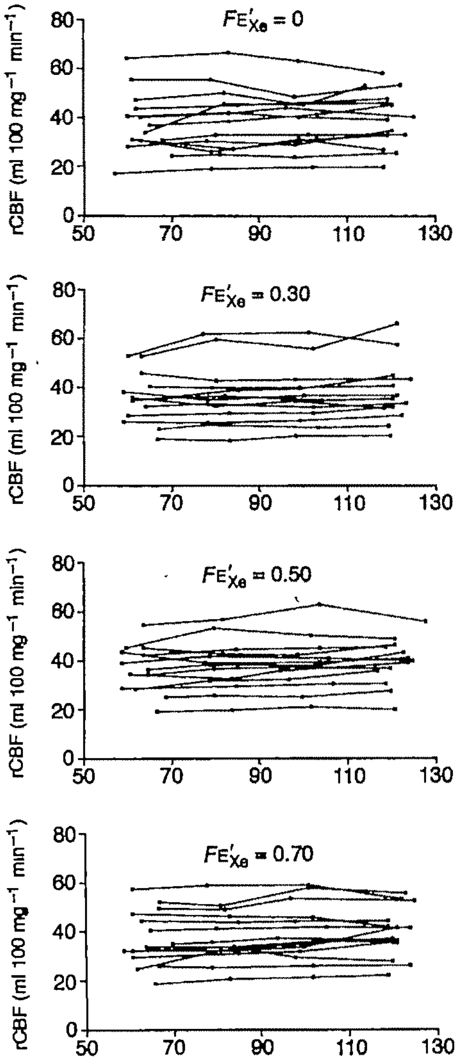


Fig 1 Regional cerebral blood flow (rCBF) as a function of different end-tidal fractions of xenon ($F\text{E}'_{\text{Xe}}$) of 0, 0.30, 0.50 and 0.70

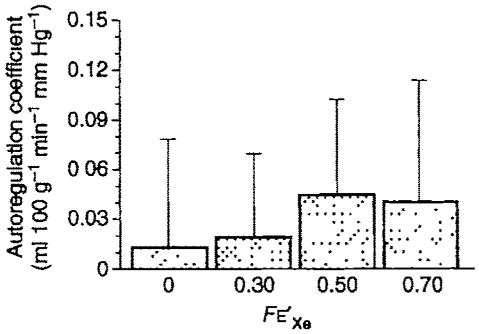


Fig 2 Autoregulatory coefficient (mean(SD)) at each respective end-tidal fraction of xenon ($F\text{E}'_{\text{Xe}}$)

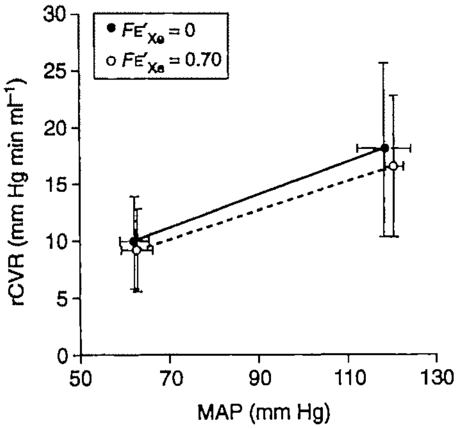


Fig 3 Regional cerebrovascular resistance (rCVR) during end-tidal fractions of xenon ($F\text{E}'_{\text{Xe}}$) of 0 and 0.70 (mean(SD))

rCBF as a function of MAP during end-tidal xenon fractions of 0–0.70. rCBF did not change with MAP manipulations. The autoregulation coefficient at $F\text{E}'_{\text{Xe}}=0$ was mean 0.031 (SD 0.065) ml min^{-1} 100 g^{-1} mm Hg^{-1}. The increase in the autoregulation coefficient was significantly less than 0.15 ml min^{-1} 100 g^{-1} mm Hg^{-1} with each individual end-tidal xenon fraction ($P<0.0001$) (Fig. 2).

Multiple regression analysis revealed no significant effect of $F\text{E}'_{\text{Xe}}$ or the interaction term (MAP×$F\text{E}'_{\text{Xe}}$) on SSP. SSP was significantly increased at higher MAP levels (SSP (mm Hg)=3.6+0.028×MAP (mm Hg); $r=0.164$; $P=0.0116$). rCVR increased with increases in MAP (Fig. 3), with no effect of $F\text{E}'_{\text{Xe}}$ or the interaction term (MAP×$F\text{E}'_{\text{Xe}}$) (rCVR (mm Hg min ml^{-1})=0.53–0.15×MAP (mm Hg); $r=0.485$; $P<0.0001$) according to multiple regression analysis.

To prove the stability of the model, carbon dioxide reactivity was measured approximately 30 min before (1.673 (SD 0.649) ml min^{-1} 100 g^{-1} mm Hg^{-1}) and 1 h after (1.637 (SD 0.543) ml min^{-1} 100 g^{-1} mm Hg^{-1}) the autoregulation tests. Carbon dioxide reactivity did not differ significantly.

Discussion

We have shown that end-tidal xenon fractions of 0.30, 0.50 and 0.70 had no effect on rCBF in pigs sedated with propofol. Similarly, autoregulation was not impaired by xenon. These data are consistent with the view that xenon is an inert compound with negligible systemic and cerebrovascular effects.

There is considerable controversy regarding the effects of xenon on CBF. Studies in awake, spontaneously breathing rats inhaling 40–80% xenon for 1–2 min showed an increase in CBF of up to 196%.[10] In awake, healthy volunteers, inhalation of 35% xenon for 2.5 or 3.5 min caused an increase in CBF of 23% and 19%, respectively.[12] In contrast, CBF did not change after 10 min of inhalation of 30–50% xenon in baboons undergoing mechanical ventilation.[16] Similarly, 80% xenon had no effect on CBF within the first 2 min of administration[16] while CBF decreased after 10 min. This was interpreted as the anaesthetic effect of the compound. This view is supported by an investigation in baboons where 35% xenon initially increased and then decreased CBF, 24 min after inhalation.[11] These inconsistent results may be related to differences in study design. Experiments showing increases in CBF allowed less than 5 min of equilibration of xenon before the CBF measurements, as this is mandatory for xenon enhanced CT scans. However, the grey matter of the brain reaches saturation within about 5 min of xenon inhalation[17] and saturation of the white matter may take as long as 30 min.[17] Thus the impact of xenon inhalation for anaesthetic use on CBF cannot be assessed with an equilibration period of less than 5 min.

In addition, inhalation of xenon may induce stress in spontaneously breathing, awake subjects which in turn increases CBF,[18] as an increase in respiratory work occurs as a function of the weight increase of the inspiratory gas mixture (>300%) when adding 70% xenon.[10] In our study, xenon had no significant effect on CBF when administered to animals sedated with propofol and undergoing mechanical ventilation. Thus any additional effect of increasing respiratory work or excitation by the onset of xenon-induced anaesthesia can be ignored. This is consistent with studies in sedated and mechanically ventilated monkeys[14] and baboons[17] where CBF did not change when xenon was administered. In summary, these data indicate that xenon had no effect on CBF in non-stressed animals if physiological variables were controlled.

Autoregulation is defined as the ability to maintain CBF constant despite alterations in MAP or CPP. In sedated baboons undergoing mechanical ventilation, CBF autoregulation tested using a blood withdrawal/infusion regimen, was intact when 30–35% xenon was administered.[19] In contrast, a study in awake, paralysed and mechanically ventilated baboons showed an increase in CBF during inhalation of 35% xenon and a decrease in MAP of 25%. In that study, MAP was manipulated using an infusion of sodium nitroprusside.[11] As nitroprusside directly reduces cerebrovascular tone, the results of this study are difficult to interpret. In our study, a mechanical arterial pressure manipulation was used to exclude pharmacological interference, and autoregulation was intact within the MAP range 60–120 mm Hg, as indicated by an increase in the autoregulation coefficient of less than 0.15 ml min^{-1} 100 g^{-1} mm Hg^{-1} at any given xenon fraction. As autoregulation is an expression of constriction or dilatation of the cerebral vessels in response to changes in MAP, CVR can also be used to represent the dynamics of CBF autoregulation. During our study, CVR was reduced in a pressure-dependent manner which relates intact cerebrovascular dilatation to decreases in input pressure.

Propofol infusion was used to maintain background anaesthesia. This may be a confounding factor as propofol decreases cerebrovascular tone which may modulate the dynamic response of brain vessels to vasoactive stimuli.[20] However, baseline CVR does not change when propofol is infused in concentrations of less than 3 mg kg^{-1} h^{-1}.[21] In addition, higher concentrations of propofol (8–12 mg kg^{-1} h^{-1}) did not impair CBF autoregulation in pigs.[22] This suggests that the propofol background sedation used here (4 mg kg^{-1} h^{-1}) did not modulate the cerebrovascular responses to changes in MAP or the end-tidal xenon fractions under steady state conditions.

The animal model chosen for this investigation was established according to Stange, Lagerkranser and Sollevi[23] and is based on the sinus outflow technique described by Michenfelder, Messick and Theye.[24] It allows continuous monitoring of blood flow of the frontal hemispheres (rCBF).[25] [26] In principle, small amounts of extracranial shunts affecting the measurements cannot be excluded. However, these influences on rCBF measurement were kept to a minimum by coagulating the surface of the exposed bone and sealing it with bone wax.[23] During our study, extracranial stains of ink were not observed in any animal, suggesting that contamination of the superior sagittal sinus with extracranial blood was insignificant.

The finding of no changes in CBF cannot be attributed to the insensitivity of our preparation as the ability of the sinus outflow technique to measure alterations was confirmed by testing carbon dioxide reactivity before and after all measurements. The range of CBF observed was caused mainly by varying proportions of cortical and subcortical tissue as a result of different positions of the sinus outflow shunt. In addition, difficulties in the exact quantification of the amount of ink-stained tissue may generate this variability. However, this variability occurred between subjects but not within individual animals (Fig. 1). Taking this into account, statistical analyses were performed predominantly on intra-individual changes.

In summary, we found that xenon, in a potential clinical set-up with propofol background sedation, had no effect on rCBF, autoregulation or baseline cerebrovascular tone, which determines the autoregulatory reserve. This suggests that xenon inhalation may be a useful alternative to nitrous oxide, especially in neurosurgical patients.

References

1 Nakata Y, Goto T, Morita S. Comparison of inhalation inductions with xenon and sevoflurane. *Acta Anaesthesiol Scand* 1997; **41**: 1157–61

2 Goto T, Saito H, Nakata Y, Uezono S, Ichinose F, Morita S. Emergence times from xenon anaesthesia are independent of the duration of anaesthesia. *Br J Anaesth* 1997; **79**: 595–9

3 Goto T, Saito H, Shinkai M, Nakata Y, Ichinose F, Morita S. Xenon provides faster emergence from anesthesia than does nitrous oxide–sevoflurane or nitrous oxide–isoflurane. *Anesthesiology* 1997; **86**. 1273–8

4 Luttropp HH, Romner B, Perhag L, *et al.* Left ventricular performance and cerebral haemodynamics during xenon anaesthesia. A transoesophageal echocardiography and transcranial Doppler sonography study. A minimal-flow system for xenon anaesthesia. *Anaesthesia* 1993, **48**: 1045–9

5 Boomsma F, Rupreht J, Man in't Veld AJ, de Jong FH, Dzoljic M, Lachmann B. Haemodynamic and neurohumoral effects of xenon anaesthesia. A comparison with nitrous oxide. *Anaesthesia* 1990; **45**: 273–8

6 Lachmann B, Armbruster S, Schairer W, *et al.* Safety and efficacy of xenon in routine use as an inhalational anaesthetic *Lancet* 1990; **335**: 1413–15

7 Marx T, Froeba G, Wagner D, Baeder S, Goertz A, Georgieff M. Effects on haemodynamics and catecholamine release of xenon anaesthesia compared with total i.v. anaesthesia in the pig. *Br J Anaesth* 1997; **78**: 326–7

8 Reinstrup P, Ryding E, Algotsson L, Berntman L, Uski T. Regional cerebral blood flow (SPECT) during anaesthesia with isoflurane and nitrous oxide in humans. *Br J Anaesth* 1997; **78**: 407–11

9 Gur D, Yonas H, Jackson DL, *et al.* Measurement of cerebral blood flow during xenon inhalation as measured by the microspheres method. *Stroke* 1985; **16**: 871–4

10 Junck L, Dhawan V, Thaler HT, Rottenberg DA. Effects of xenon and krypton on regional cerebral blood flow in the rat. *J Cereb Blood Flow Metab* 1985; **5**: 126–32

11 Hartmann A, Wassman H, Czernicki Z, Dettmers C, Schumacher HW, Tsuda Y. Effect of stable xenon in room air on regional cerebral blood flow and electroencephalogram in normal baboons. *Stroke* 1987; **18**: 643–8

12 Hartmann A, Dettmers C, Schuier FJ, Wassmann HD, Schumacher HW. Effect of stable xenon on regional cerebral blood flow and the electroencephalogram in normal volunteers. *Stroke* 1991; **22**: 182–9

13 Obrist WD, Zhang Z, Yonas H. Effect of xenon-induced flow activation on xenon-enhanced computed tomography cerebral blood flow calculations. *J Cereb Blood Flow Metab* 1998; **18**· 1192–5

14 Yao LP, Bandres J, Nemoto EM, Boston JR, Darby JM, Yonas H. Effect of 33% xenon inhalation on whole-brain blood flow and metabolism in awake and fentanyl-anesthetized monkeys. *Stroke* 1992; **23**: 69–74

15 Giller CA, Purdy P, Lindstrom WW. Effects of inhaled stable xenon on cerebral blood flow velocity. *Am J Neuroradiol* 1990; **11**: 177–82

16 Meyer JS, Hayman LA, Yamamoto M, Sakai F, Nakajima S. Local cerebral blood flow measured by CT after stable xenon inhalation. *Am J Roentgenol* 1980; **135**: 239–51

17 Fatouros PP, Wist AO, Kishore PR, *et al.* Xenon/computed tomography cerebral blood flow measurements. Methods and accuracy. *Invest Radiol* 1987; **22**: 705–12

18 Bryan RM jr. Cerebral blood flow and energy metabolism during stress. *Am J Physiol* 1990, **259**: H269–80

19 Wolfson SK jr, Yonas H, Gur D, Cook EE, Greenberg J, Brenner RP. Autoregulation remains intact during stable xenon inhalation in the baboon. *Adv Exp Med Biol* 1990; **277**: 865–72

20 Eng C, Lam AM, Mayberg TS, Lee C, Mathisen T. The influence of propofol with and without nitrous oxide on cerebral blood flow velocity and CO_2 reactivity in humans. *Anesthesiology* 1992; **77**: 872–9

21 Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. *Anesth Analg* 1990; **71**. 49–54

22 Lagerkranser M, Stange K, Sollevi A. Effects of propofol on cerebral blood flow, metabolism, and cerebral autoregulation in the anesthetized pig *J Neurosurg Anesthesiol* 1997; **9**: 188–93

23 Stange K, Lagerkranser M, Sollevi A. Effect of adenosine-induced hypotension on the cerebral autoregulation in the anesthetized pig. *Acta Anaesthesiol Scand* 1989, **33** 450–7

24 Michenfelder JD, Messick JM jr, Theye RA. Simultaneous cerebral blood flow measured by direct and indirect methods. *J Surg Res* 1968; **8**· 475–81

25 Stange K, Lagerkranser M, Sollevi A Nimodipine does not affect the cerebral autoregulatory response in the anesthetized pig. *J Neurosurg Anesthesiol* 1994; **6**: 116–21

26 Stange K, Lagerkranser M, Sollevi A. Nitroprusside-induced hypotension and cerebrovascular autoregulation in the anesthetized pig. *Anesth Analg* 1991; **73**: 745–52

British Journal of Anaesthesia 84 (2)· 226–35 (2000)

BJA

REVIEW ARTICLE

Measurement of blood volume in surgical and intensive care practice

J. G. Jones[1]* and C. A. J. Wardrop[2]

[1]*School of Biological Sciences, Cardiff University, PO Box 911, Cardiff CF1 3US, UK.* [2]*Department of Haematology, University of Wales College of Medicine, Heath Park Cardiff CF4 4XN, UK*

**Corresponding author*

Br J Anaesth 2000; **84**: 226–35

Keywords: blood, volume; blood, PCV; measurement techniques, blood volume; intensive care

Circulating blood volume (CBV) is an important, but often unmeasured, variable in patients undergoing major surgery and in intensive care.[22] Severe volume depletion leads to clearly recognizable clinical shock that requires urgent intervention.[100] Smaller volume depletion, however, may have no noticeable effect on circulation and arterial pressure as vasoconstriction assists in the redistribution of blood to vital organs. Consequently, reduced blood flow to several organs, such as the skin, kidney and gastrointestinal tract, renders them ischaemic to maintain a normal arterial pressure (i.e. normotensive compensated shock).[47] Although CBV is not usually measured, a high proportion of patients undergoing cardiac surgery, and those in intensive care units or with sepsis, are thought to have this form of compensated shock and lack adequate resuscitation.[22] This lack of perfusion and oxygenation leads to gut mucosal ischaemia[99] with a resulting decrease in gastric intramucosal pH that is an important predictor of outcome in critical care patients.[7 17 23 38 79]

Untreated hypovolaemia also leads to exaggerated inflammatory and immune responses that have an effect on tissues distant from the primary ischaemic site.[49] The results are similar to the systemic inflammatory response syndrome and share many of the clinical features of bacterial sepsis.[34] Clearly, in a patient already compromised by trauma, relatively small volume depletions can have serious and unexpected physiological consequences. Evidence shows that preoperative expansion of plasma volume with colloid, aiming to optimize the circulating blood volume, helps to prevent the onset of a low gastric intramucosal pH, thereby reducing the incidence of gut mucosal hypoperfusion and improving clinical outcome.[73 85] Traditionally, routine monitoring of central venous pressure, pulmonary artery wedge pressure, cardiac output and urine output have been guides in fluid or blood transfusion, or both, but are not reliable indicators of CBV.[84] These surrogate measures are unreliable because mechanisms that retain the relationship between red cell volume (RCV), plasma volume (PV) and CBV may not always operate effectively and changes in CBV are masked by selective vasoconstriction. The physiological mechanisms that control CBV are complex and encompass independent controls of RCV and PV. In isolation, the principles involved in each of these processes are understood and appear to be designed to maintain RCV and PV with an overall influence on CBV through pressure-mediated control of PV.

In this review, we summarize these physiological mechanisms and discuss laboratory measures of RCV, PV and CBV.

Physiological control of blood volume

Control of red cell volume in health

Erythropoiesis, the production of red blood cells, is under the control of the hormone erythropoietin. The amount of erythropoietin in plasma is regulated by blood oxygen tension and affected by the concentration of haemoglobin, arterial oxygen tension, haemoglobin–oxygen affinity and renal blood flow.[58] The oxygen sensor is believed to be a haem protein synthesized largely, but not exclusively, in the kidney. The deoxygenated form of this protein is believed to enhance erythropoietin synthesis by stimulating the erythropoietin gene, and it may stabilize the resulting mRNA.[32 33] The kidney extracts very little oxygen from the blood and therefore operates at the ‘top end’ of the haemoglobin–oxygen binding curve and small changes in oxygen extraction and/or oxygen delivery produce large changes in oxygen tension in plasma. The kidney is an ideal organ for locating the sensors for detecting a deficit in oxygen supply.

Control of plasma volume in health

Water accounts for approximately 60% of body weight and is contained within two recognizable volumes of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

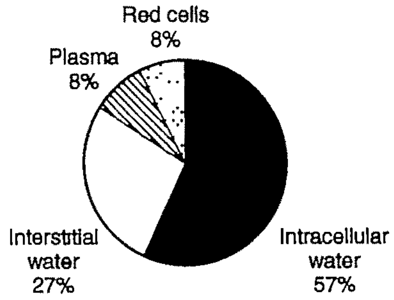


Fig 1 Proportion of body water in intravascular and extravascular compartments. The total volume is approximately 42 litre.

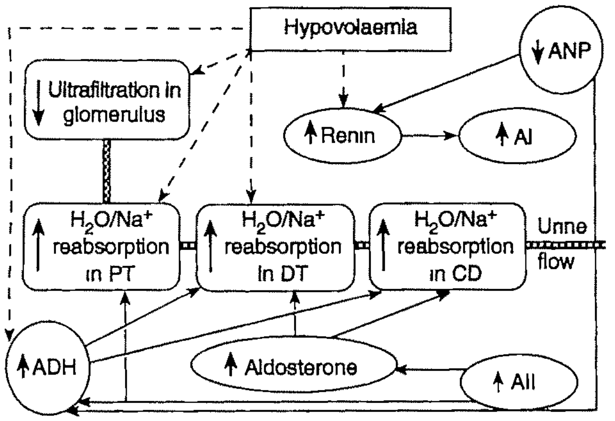

Hypovolaemia
Ultrafiltration in glomerulus
↓ANP
↑Renin
↑AI
H_2O/Na^+ reabsorption in PT
H_2O/Na^+ reabsorption in DT
H_2O/Na^+ reabsorption in CD
Urine flow
↑ADH
↑Aldosterone
↑AII

Fig 2 Mechanisms involved in the physiological response of a nephron to hypovolaemia. The overall effect is a reduction in urine flow. Hormonal responses (arrows with continuous lines) and sympathetic nerve responses (arrows with broken lines) are indicated. PT=Proximal tubule; DT=distal tubule; CD=collecting duct, AI=angiotensin I; AII=angiotensin II; and ANP=atrial natriuretic peptide.

distribution, the intracellular and extracellular fluid. The extracellular fluid is subdivided further into interstitial fluid, red blood cells and plasma (Fig. 1). In normal circumstances, the water compartments of the body maintain a constant volume and concentration of solute, although water is constantly in dynamic equilibrium. Renal function determines body sodium and water content via the relation between arterial pressure and urinary sodium or volume output.[92] Sensitive and powerful homeostatic mechanisms directed towards excretion or retention of sodium and water come into effect when PV exceeds or falls below its normal level. Both neural and hormonal mechanisms are involved in the regulation of PV and the concerted response to hypovolaemia is summarized in Figure 2.

Control of interstitial fluid volume in health

The net distribution of water and electrolytes between plasma and interstitial fluid is governed by differences in hydrostatic and osmotic pressures across the capillary bed, the permeability of the capillary wall to water and solutes, and the rapid removal of interstitial fluid via the lymph. Mobilization of interstitial fluid from organs such as skeletal muscle and skin with large tissue mass and fluid reservoirs, contributes in an important way to restoration of PV after blood loss.[62]

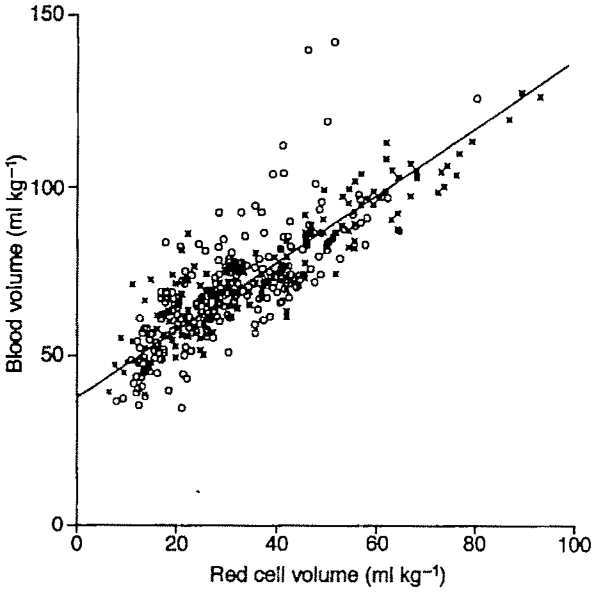


Fig 3 Relationship between circulating blood volume and red cell volume in a variety of hospital patients in adults (x) and neonates (O) Reproduced from *Br J Haematol* 1990, **76**: 288–294 (with permission) [60]

Blood volume and the vasculature

These collective control mechanisms seem to be designed to maintain CBV through independent controls of RCV and PV. However, in post-trauma patients, sepsis and inflammation suppress erythropoiesis and impaired vascular endothelial integrity leads to loss of plasma water, salts and small proteins, such as albumin. In these circumstances, a near normal PCV may well mask significant hypovolaemia[99] and single point estimations of PCV do not correlate with heart rate or cardiac output.[1, 15, 50] Even before the onset of these complications, the physiological control mechanisms for RCV and PV may not maintain an adequate CBV. A large volume of data[5, 60] shows that, in a range of patients with haematological abnormalities, there was a linear relationship between RCV and CBV (Fig. 3). Although there was a large degree of scatter around this relationship, there was no evidence of compensatory changes to maintain CBV in response to alterations in RCV. Hence baroreceptor responses that lead to changes in PV may not provide ultimate control of CBV.

Whatever the uncertainty about control mechanisms for maintaining CBV, there is no doubt that the volume of the vasculature can be altered to accommodate changes in CBV. Approximately 50–60% of the circulating blood is contained within the venous compartment of the vascular system. Changes in the compliance of veins, particularly those in the skin and splanchnic organs, maintain the correct relationship between vascular space and blood volume, ensuring an adequate return of blood to the heart. The splanchnic circulation has been described as an autologous blood bank drawn upon when blood volume is depleted.[55] Conversely, if blood is withdrawn from the peripheral circulation, the splanchnic veins, acting as a deposit account, expand to accommodate the extra-centralized blood and protect the heart from fluid overload.[55] Hence in response to a reduction in CBV, an uneven decrease in venous compliance occurs, leading to redistribution of blood flow through organs such as the heart and brain which helps to protect them from oxygen deprivation. In cases of chronic anaemia, this protection mechanism allows a significant reduction in RCV (and hence CBV) before major signs of tissue hypoxia are manifested. Theoretical considerations have led to a prediction of a critical RCV, above which no major biological responses may be apparent.[60] Clinical data[50] identify 25 ml kg^{-1} as the critical level for RCV, below which cardiac output in preterm anaemic neonates is increased at rest. This corresponds to a PCV of approximately 0.28 that is adequate to supply the basic needs for oxygen in a patient at rest and unchallenged. However, this critical RCV may be coupled with hypovolaemia (Fig. 3) and associated with a maximal vasoconstriction response to protect vital organs. An increased demand for oxygen by other tissues is not met and a spiral of ischaemia, acidosis, general inflammatory response and increased cardiac output results in a further demand for oxygen that cannot be met by a PCV of approximately 0.3. So what is an optimum PCV?

Concept of an optimum packed cell volume

As mentioned above, there is an unspoken assumption that the loss of red cells does not lead to a long-term decrease in blood volume. Calculations based on this assumption and the relationship between RCV and viscosity on the one hand and oxygen content of blood on the other, lead to an optimum PCV that is close to that observed in healthy adults and neonates.[66] Hence both an increase and a decrease in the concentration of haemoglobin can compromise oxygen delivery. For example, in the long term, an increased PCV is a recognized risk factor in cardiovascular and cerebral disease.[67 90] These viscosity-related dangers of a chronic increased PCV, together with risks of infection from donated blood, has led to a cautious approach to blood transfusions in clinical practice. For similar reasons, haemodilution therapy, to anaemic levels, has been proposed as a treatment to improve cerebral blood flow and aid recovery from an ischaemic insult to the brain.[44 61 88] The results of clinical studies of this intervention have been mixed but good outcomes have been achieved by normovolaemic dilution to a PCV of approximately 0.35.[35] A similar degree of haemodilution is claimed to be of benefit in the treatment of peripheral occlusive arterial disease[20 48] and before cardiac surgery.[73] Again, an increase in haemoglobin, by transfusion of packed red cells, proved detrimental to some but not all critical care patients.[45]

In general, quoted values for optimum PCV lie within a broad range from 0.30 to 0.56. These disparate values have been derived by a variety of theoretical predictions or measurements *in vitro* and *in vivo* under various clinical conditions.[48] They do not indicate a single unique value for any individual or for all eventualities. It could be argued that a healthy male adult has a PCV of 0.45 which has been evolved as optimum for living at sea level by various physiological factors which control RCV, PV and oxygen delivery. Prolonged training by an endurance athlete leads to an increase in PV and decrease in PCV to meet the new pattern of required oxygen delivery. This hypervolaemic haemodilution increases maximum oxygen consumption in this type of athlete by about two-fold.[78] However, short-term ambitions to win a race may lead to the practice of blood doping—an artificial increase in PCV by blood transfusion or by self-medication with recombinant erythropoietin. This leads to improved physical performance[94] but poses a risk to the individual. Hence the attractive concept of an optimum PCV is valid only for one particular and chosen end-point. It is not a universal truth and has been described as a complex issue to which there is no simple answer.[55]

In a clinical situation, it is necessary to strike an appropriate balance between the ideal of maximum efficiency during prolonged physical activity and that of optimum microcirculatory flow in the affected tissue.[80] This balance depends on the oxygen requirement of the patient and is expected to shift to higher values of PCV with improvement in health and an increased requirement for oxygen to meet renewed physical activity. A target PCV of 0.33 may therefore be desirable in supine patients to improve impaired intracranial blood flow. It may also be an acceptable compromise in patients with intermittent claudication where an improved capacity for mild physical activity is achieved by reducing the oxygen reserve required for what is anyway an unattainable level of strenuous exercise. However, this level of reduction in oxygen carrying capacity may not be acceptable in all critical care patients as a good reserve of oxygen may be needed to combat life-threatening conditions such as septic shock and to meet the increased needs of the myocardium and respiratory muscle. The optimum haemoglobin concentration therefore depends on the oxygen requirement and this depends on CBV. Euvolaemic experimental animals can tolerate a 75% reduction in the concentration of haemoglobin but a reduction of only 25% when anaemia is accompanied by hypovolaemia.[12 13] These considerations may account for conflicting evidence relating to the advantages/disadvantages of haemodilution/transfusion in patients who are critically ill.[15 68 69 71 73] Thus it has been argued that, in the diagnosis and treatment of anaemia/hypovolaemia, no decision can be entirely rational without direct knowledge of CBV.[47 100]

Laboratory measurement of blood volume

Experimental measures of body water are based on dilution of a suitably administered compound. Water passes freely between the various compartments of the body and total body water is calculated from the concentration, after equilibration, of labelled water (e.g. ^{3}H-water). In principle, the volume of any compartment can be calculated from the measured concentration of an administered marker that is confined to that compartment. Measurement of PV requires water soluble markers that are confined, at least initially, to the plasma space, while measurement of RCV requires markers that are specific for red blood cells—usually compounds that interact with haemoglobin or the unique proteins of the red cell membrane.

Measurement of plasma volume

Historical perspective

Early methods of measuring CBV were based on an assessment of PV and the assumption that the PCV of peripheral blood is the same as that in the body as a whole. The development of these techniques for measuring CBV has a long history and a casual observer may be forgiven for believing it to be tediously slow. A review of 60 yr of progress in this field using a variety of techniques appeared as long ago as 1917.[77] The first attempt at a dilution method of measuring CBV is attributed to Vierordt in 1858 who bled an animal, waited until he thought the 'tissue juices' had restored the lost fluid and then determined the dilution of the red cells.[70] CBV was then calculated on the assumption that the withdrawn volume was replaced by plasma before significant regeneration of red blood cells. This method was found to give equivalent results to those obtained by exsanguination in rabbits.[18] In those early days, CBV was also measured from a decrease in PCV, the specific gravity of blood or the concentration of plasma solids, haemoglobin or red cells after injection of a known volume of water, saline, serum or blood.[70 83] However, the limitations of these methods were recognized in 1918 because of '7 the extreme rapidity with which injected water and salt solutions leave the blood stream'.[70] There followed a series of methods which were based on the dilution of molecules that would not leave the bloodstream so rapidly. Chosen molecules included tetanus antitoxin, the dye Vital Red and a large polysaccharide derived from acacia gum.[70] With any dilution method the volume of blood is calculated from:

$$\text{Volume } \textit{in vivo} = \frac{\text{Volume injected} \times \text{concentration of marker}}{\text{Concentration of marker in blood sample}}$$

This relationship gives PV or CBV depending on whether the concentration *in vivo* is expressed per ml of plasma or blood. This general approach to CBV measurement remains the same today and many of the same concerns continue to be relevant.

Volume of distribution of albumin

The use of Vital Red as a plasma marker has been extended to other dyes with a high affinity for plasma proteins, the most highly investigated being T-1824 or Evans Blue.[14] This azo dye was chosen in a systematic survey of approximately 60 dyes and became the standard plasma marker until the use of radioisotopes was developed some 20 yr later. Evans Blue was considered to be a label for the protein albumin and an ideal marker for plasma space. It can be measured directly in plasma from absorption of light at 620 nm.[29 37] This direct method can be unreliable when the plasma is turbid or contaminated by haemoglobin. Indirect methods are available which separate the dye from albumin into a suitable solvent.[25 57] This dye dilution technique has been used to estimate the PV at birth of infants with haemolytic disease[75] and in respiratory distress syndrome.[64] The use of this dye in humans was eventually abandoned in view of reports of sensitivity reactions and unacceptable levels of patient discolouration, in addition to a suspicion of carcinogenicity in animals. However, because of the unsuitability of radioisotopes for use in paediatrics and women of child-bearing age, there has been a resurgence in the use of Evans Blue in recent years[19 21] using a more user-friendly method that does not require a lengthy procedure of dye extraction.

The use of radioactive tracers as albumin markers began about 50 yr ago. Albumin, labelled with ^{131}iodine, was used to measure PV in dogs[30] and in humans.[25 81] The volumes of distribution of ^{131}I-albumin and Evans Blue were identical and the former became the method of choice in the absence of contraindications for its use (e.g. in pregnancy). Radiolabelled albumin has been used to estimate PV in non-viable fetuses at the time of surgical abortion,[72] in newborn infants[102 95] and in critically ill children.[64 65] Some practical advantages are gained if the short-lived ^{131}I (half-life 8.1 days) is replaced with the more stable ^{125}I (half-life 60 days). The inherent dangers of radioactive isotopes *in vivo* kept the need open for a suitable chromophoric label for plasma proteins and again albumin became the target.

Indocyanine green (ICG) is a dye used for assessing cardiac output in surgical patients and has proved useful in assessing PV in rabbits[63] and humans.[9] The concentration of the dye in plasma can be determined from light absorption at 805 nm. Although not particularly stable,[28 46] it has been used successfully for measuring PV in adults[10 41 42] and in neonates.[4] The dye is bound mainly to albumin, eliminated rapidly through the liver (plasma half-life approximately 3 min) and shows little sign of triggering adverse reactions or toxic effects.[27] The volume of distribution of ICG is comparable with that of albumin labelled with radioactive iodine[9] or Evans Blue.[42]

Yet another label for plasma albumin has been described for use *in vivo*. The sulphonyl chloride derivative of sulphorhodamine 101 (Texas Red) is a useful fluorescent probe that can be attached to albumin. The complex with bovine albumin (TR-A) is available commercially and has been used successfully to measure PV in rats.[31] PV, determined in this way, was typically approximately 10%

higher than when determined by ^{125}I-bovine albumin; no reasons for this difference were offered.

Volume of distribution of other potential plasma markers in health and disease

Knowledge of PV is likely to be important in patients with post-surgical compensated shock when the integrity of the vascular endothelium may well be compromised.[34 43] A possible objection to equating the volume of distribution of albumin with PV is that it also equilibrates with interstitial water to a concentration that is approximately 10% of that in plasma. However, the interstitial space is approximately six times greater than PV and therefore contains about 40% of the body albumin. However, unless equilibration is instantaneous, the error involved in equating PV to albumin space depends on the rate at which albumin equilibrates with interstitial water and not the available volume. If this rate is slow, compared with the time required for adequate mixing of the administered dose in the circulatory system, and sequential measurements are made of plasma concentration, then the error should be zero. Approximately 5% of plasma albumin crosses into extravascular space every hour and this increases to 15% per hour in septic shock.[24] This rate of loss is not large enough to invalidate a correction procedure based on sequential measures of albumin label in plasma. After all, 23% of administered ICG is lost from plasma in 1 min (plasma half-life approximately 3 min) but its volume of distribution is very similar to that of more stable labels of albumin. Again, during the first hour after administration, hydroxyethyl starch disappears from plasma at a rate of 23% per hour[91] but its volume of distribution is close to that of red blood cells.[91 93] Nevertheless, despite the measured low rate of loss of albumin, it is generally accepted that the measured volume of distribution of albumin exceeds PV and the difference is exaggerated when capillary integrity is impaired. This error must reflect the amount of albumin lost from plasma during the first 5 min or so and not its measurable rate of loss over the ensuing 30 min. So whatever the problem, it happens rapidly and its rate cannot be measured. There are three theoretical possibilities to explain the apparent loss of albumin from plasma that precedes its free flow into interstitial water.

1. There may be a small volume of extravascular water (about 1% of interstitial water) that is immediately accessible to albumin and is increased in some clinical conditions.
2. Albumin may be in rapid equilibrium with receptors on endothelial cells and these are increased in number by an inflammatory response.
3. When capillary permeability is increased, the concentration of circulating albumin is decreased. In these circumstances the proportion of albumin bound to a fixed number of receptors increases and the corresponding lower concentration of free albumin yields a false high value for its volume of distribution.

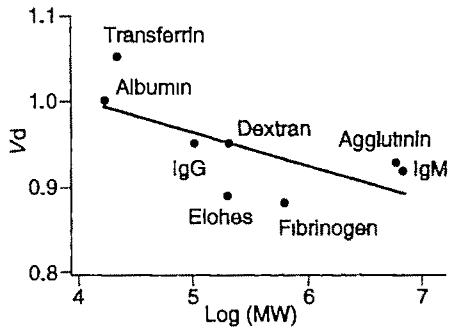


Fig 4 Effect of molecular weight on the volume of distribution (V_d) of molecules *in vivo*.

Whatever the reason, albumin is not an ideal molecule for measuring PV. The early use of tetanus antitoxin as a plasma marker points the way to several alternatives to albumin as possible plasma markers. The volume of distribution of various globulins is less than that of albumin by 2.5–4.7% in adults[2 3] and 8.0% in neonates.[87] The volume of distribution of ^{131}I-labelled cold agglutinin molecules is reported to be lower than that of albumin and the difference is thought to be greater in clinical conditions with increased capillary permeability.[96] The use of polysaccharides, pioneered by use of acacia gum,[70] has been extended to the use of various dextrans as true plasma markers in dogs and humans.[82] The results with large and highly hydrated polysaccharides lend support to the belief in the unsuitability of albumin as a plasma marker in clinical investigations. The volume of distribution of dextrans was found to be slightly less than that of albumin in normal subjects but significantly less in cardiac patients and in patients with oedema.[56 57] Another study[91] compared the volume of distribution of radiolabelled albumin with hydroxyethyl starch in 18 subjects and found a 7% greater volume of distribution for the protein. In preoperative elective neurosurgical patients, there was good agreement between CBV determined with hydroxyethyl starch and that estimated with the haemoglobin label, carbon monoxide.[93]

These collective data indicate an inverse relationship between the size of any molecule and its volume of distribution *in vivo*. The size of each molecule is only loosely related to its weight. Polysaccharides are larger than proteins of the same weight as they are hydrophilic, less compact and have a larger degree of hydration. Globular proteins such as albumin, occupy a smaller volume than fibrous molecules such as the globulins and fibrinogen. Notwithstanding these variations, there is a clear correlation between the molecular weight and volume of distribution of a number of macromolecules (Fig. 4). However, the concomitant assumption that the measured volume of distribution reflects the rate at which a molecule flows from plasma to interstitial water may be erroneous. The ultimate determinant of the suitability of any plasma marker may be the availability or number of receptor sites on the surface of endothelial cells and the relationship shown in Figure 4 may be coincidental.

Measurement of red cell volume

Deliberate bleeding and subsequent estimation of the red cell concentration was used in experimental animals in 1858[70] but is not a viable alternative in clinical medicine. However, an increase in red cell concentration by blood transfusion has been used more recently after intrauterine transfusion of erythrocytes to fetuses suffering from rhesus haemolytic disease.[59, 74] The volume of blood, before the transfusion, is calculated from:

$$\mathrm{CBV}=\frac{V_d\,(\mathrm{H_d{-}H_f})+V_s(\mathrm{H_f{-}H_i})}{(\mathrm{H_f{-}H_i})}$$

where V_d=volume of donor blood, V_s=volume of sample withdrawn for analysis, $\mathrm{H_d}$=PCV of donor blood, $\mathrm{H_f}$= PCV of post-transfusion sample and $\mathrm{H_i}$=PCV of the pre-transfusion sample.

This method, applicable with any red cell transfusion, appears more attractive than any other as the volume of distribution of erythrocytes must represent the true circulating PV. However, it was appreciated as long ago as 1918 that with this method, the volumes transfused are relatively large and may initiate compensatory extravasation of plasma.[70] This movement of fluid out of the vasculature into placental interstitial space is particularly large and rapid in ovine[8] and human[98] fetuses and the transfused red cell method leads to underestimation of CBV. In contrast, methods based on dilution of albumin grossly overestimate fetal CBV.[8]

Radioactive labelling of red blood cells began with ^{32}P-labelling[39] but ^{51}Cr soon became the standard labelling isotope.[36] Pentavalent chromium, administered as $\mathrm{Na_2CrO_4}$, enters red cells and trivalent chromium binds to β chains of haemoglobin to form a complex, thereby becoming a suitable red cell label. Other radioisotopes, such as ^{99m}Tc, ^{111}In and ^{113m}In, may eventually replace ^{51}Cr as they have a lower activity. The main advantages of ^{51}Cr are that the labelling procedure is simple and, as only 0.5% of the label is lost from red cells during the first 60 min after injection, no correction has to be made for this, even in patients with a prolonged mixing time. The relatively long half-life of ^{51}Cr (27.7 days) means that red cell survival can be followed over a period of weeks if needed. The chief advantage of ^{99m}Tc, ^{111}In and ^{113m}In over ^{51}Cr, apart from lower radioactivity, is that their short half-life enables repeated estimates to be made in the same subject at short intervals. A minor disadvantage of these short-lived isotopes is that radioactivity must be counted within 6–12 h from the time of injection and a correction must be made for radioactive decay between the counting of one sample and another. Also, in practice, labelling red cells is not quite as simple with ^{99m}Tc and ^{113m}In as it is with ^{51}Cr. The International Committee for Standardisation in Haematology provides standardization of techniques using radionuclides to measure RCV and PV.[52, 53] These important guidelines emphasize that: 'There is no practical definitive reference method available for measuring either RCV or PV, but the methods to be described have been designated as ICSH-selected methods on the basis of their reliability'. As in the case of measurement of PV, there is a need for non-radioactive labels for human red blood cells.

Carbon monoxide. Dilution of inhaled carbon monoxide as a means of measuring RCV has been used and modified for 100 yr.[16, 40, 86] In the critical care clinical environment, the non-radioactive carbon monoxide method offers the potential for CBV measurements, as instruments such as CO oximeters may be readily available In dogs, the results agree with those measured by ^{51}Cr labelling and in humans, with those predicted by standardized nomograms.[26] Disadvantages of the CO method include the use of complex gas circuitry, binding of CO to other haem proteins and a small impairment in oxygen delivery.[16]

Biotin. A derivative of the water-soluble vitamin biotin is another useful label for red blood cells which has been used successfully in animals, human adults and neonates.[11, 51, 89] Biotin-labelled cells can be detected after secondary labelling with a fluorescent marker, streptavidin-FITC. Fluorescent cells are separated from non-labelled cells and counted using a fluorescence activated cell sorter (FACS). RCV is then calculated from:

$$\mathrm{RCV}=\frac{\text{Cells injected}\times\%\text{labelled}\times\text{MCV}}{\%\text{ of cells labelled in sample}}$$

Dilution of fetal haemoglobin. A novel dilution technique for measuring RCV[76] is only applicable in neonates and fetuses requiring blood transfusion. In this technique, dilution of fetal haemoglobin in the recipient blood by adult haemoglobin in the donor blood forms the basis of the method. The percent of fetal haemoglobin is measured before and after transfusion using alkali denaturation to distinguish between the two forms of haemoglobin. RCV is then calculated from:

$$\mathrm{RCV}=\frac{\text{Volume transfused}\times\text{post.Tx}\%\text{F}}{(\text{Pre.Tx}\%\text{F}-\text{Post.Tx}\%\text{F})}$$

Dilution of fetal haemoglobin (HbF) is an example of a general principle which can be used in cases where one person is transfused blood from another person. In theory, any measurable difference between the recipient and donor blood can be exploited as a basis for a dilution method for measuring RCV. The difference in IgM levels between neonatal plasma and donated adult plasma has been used to measure PV in neonates.[87] Transfusion of red cells is invariably intended to improve anaemia and an inevitable increase is seen, indeed sought, in the PCV of the recipient's blood. This change has been used to calculate CBV in fetuses with haemolytic disease caused by RhD antibodies.[74] RCV has been measured in neonates and fetuses suffering from rhesus haemolytic disease and requiring transfusion of adult red cells.[59, 101] The method is based on dilution of RhD$^+$ cells of the recipient by D$^-$ cells of the donor blood.

The cells are labelled with human anti-D and fluorescent labelled sheep anti-human IgG. D^+ and D^- cells are then separated by fluorescence-activated cell sorting and RCV is calculated from dilution of autologous D^+ by donor D^- red cells.

Measurement of total blood volume

At the beginning of the 20th century, CBV was estimated in small mammals from the PCV of blood and calculated total haemoglobin after exsanguination of the animal.[18 77] At that time, this direct method was considered to be the most accurate means of determining blood volume yet devised.[70] It is of course limited in application as the life of the animal is sacrificed. CBV is now determined indirectly as the sum of independent measurements of PV and RCV. The recommended methods are ^{51}Cr or ^{99m}Tc as red cell markers, and radioiodine-labelled human serum albumin as a plasma marker.[53]

CBV can also be computed from measured PCV with either RCV or PV and using the relationships:

$$\text{CBV}=\frac{(\text{PV})}{(1-(\text{PCV}))}\quad\text{or CBV}=\frac{\text{RCV}}{\text{PCV}}$$

These relationships have been questioned because of the reported variable relationship between measured peripheral PCV and whole-body haematocrit (B-PCV). The quoted ratio B-PCV/PCV varies from 0.75 to 0.97 in both adults and neonates and two possible reasons have been postulated.

(1) The distribution of flowing blood cells and plasma in the microvasculature varies with the diameter of the vessel, and the PCV of blood from a peripheral vein or artery is not the same as that found in narrow capillaries or venules. A dynamic decrease in the PCV of flowing blood begins to appear in vessels of approximately 300 μm diameter and is minimal at about 10 μm (the Farhaeus effect). However, this explanation is unconvincing because less than 10% of blood is found in systemic capillaries and any difference in PCV here would have to be unrealistically large to produce the observed difference between peripheral PCV and whole-body B-PCV.

(2) B-PCV is calculated from independent measures of RCV and PV and the latter is accepted as the volume of distribution of labelled albumin. However, albumin is not confined to the circulation and its use as a plasma marker is not ideal, especially in patients with impairment of endothelial integrity. The International Committee for Standardisation in Haematology, which recommended the use of radioiodine-labelled human serum albumin as a plasma label, point out: 'There is evidence that the use of a protein with molecular weight considerably greater than albumin will give a smaller estimate of the distribution space and probably a more accurate indication of the true PV. However, in practice no suitable alternative preparations are yet available'.[53]

Table 1 Reference values for blood volume variables (ICSH, 1995). S=Surface area (m^2), age=age in years

	RCV (ml)	PV (ml)
Male	1486×S–825	1578×S
Female	1.06×age+822×S	1395×S

Traditional measurements of PV, using albumin labels, therefore provide an overestimate of true circulating PV and probably make the major contribution to the falsely low ratio of PCV/B-PCV. This is particularly true in patients with increased endothelial permeability.[96] In our view, the appropriate PCV/B-PCV ratio should always be unity.

In summary, until a suitable plasma marker is found, the use of PV to predict CBV is likely to be unsatisfactory and should be avoided. There is, however, no objective reason for rejecting RCV and PCV as a reliable method for measuring CBV. Measurements of RCV are difficult technically and/or require the use of radioisotopes. Ideally what is required is a reliable measure of PV and hydroxyethyl starch may fit the bill, even in sick patients.[91 93] However, there are technical problems. Unlabelled starch is readily available but very tedious to assay[59 91 93] while fluorescent labelled starch is easy to assay[91] but not yet available commercially.

Interpretation of measured blood volume

If possible, it would probably be best to use each individual as her/his own control. CBV during or after surgery should be compared with that before the patient became critically ill. This ideal is rarely possible and some reference values are required. The volume of blood depends on the size of the individual and also on the relative amounts of fatty and lean tissue. CBV is usually expressed in relation to body weight[6] and PV is quoted in textbooks of haematology as 45±5 ml kg^{-1} in men and women while RCV is quoted as 30±5 ml kg^{-1} in men and post-menopausal women and 25±5 ml kg^{-1} in younger women. However, because of differences in the blood supply to fatty and lean tissue, the surface area is likely to be a better baseline for comparison. The International Committee for Standardisation in Haematology has provided formulae for calculating the expected CBV in males and females.[54] These reference values are summarized in Table 1.

Summary

Clinical studies to assess the benefits of blood transfusion or haemodilution in critical illness should take account of measured CBV before, during and after intervention. As mentioned above, surrogate measures of CBV are inadequate and studies based on these[15 68 71 73] must be considered incomplete, because they cannot distinguish between effects of changes in haemoglobin concentration and changes in blood volume. The choice of a suitable technique for measuring CBV depends on the facilities available locally. In general, methods based on labelled red cells are more reliable but are technically demanding and time consuming. Those based on albumin are likely to yield false high values and this is particularly true in all patients with impaired capillary integrity. The most promising plasma marker is hydroxyethyl starch[91,93] which may be particularly useful when the polysaccharide is labelled with a fluorescent dye. Attaching fluorescein to hydroxyethyl starch is not difficult[91] and, should demand be sufficient, it may well become available from manufacturers who are already capable of providing other fluorescent polysaccharides. The clinical benefits of such a development would include more rational schedules of i.v. fluid and blood transfusion management in surgical and intensive care patients.

References

1. Alverson DC, Isken VH, Cohen RS. Effect of booster blood transfusions on oxygen utilisation in infants with bronchopulmonary dysplasia. *J Pediatr* 1988; **113**: 722–6
2. Andersen SB. Simultaneous determination of plasma volume with ^{131}I-labelled gamma globulin, ^{131}I-labelled albumin and T-1824. *Clin Sci* 1962; **23**: 221
3. Andersen SB, Gabuzda TG. Simultaneous determination of plasma volume with T-1824 and ^{131}I-labelled autologous and homologous paraprotein. *Clin Sci* 1964; **26**: 41–5
4. Anthony MY, Goodall SR, Papouli M, Levene MI. Measurement of plasma volume in neonates. *Clin Sci* 1992; **67**: 36–40
5. Bentley SA, Lewis SM. The relationship between total red cell volume and venous haematocrit. *Br J Haematol* 1976; **33**: 301–7
6. Berlin NI. Diagnosis and classification of the polycythaemias. *Semin Hematol* 1975 **12**: 339–51
7. Boldt J, Heesen M, Mukker M, Pabsdorft M, Hemplemann G. The effects of albumin versus hydroxyethyl starch solution on cardiorespiratory and circulatory variables in critically ill patients. *Anesth Analg* 1996; **83**: 254–61
8. Brace RA. Regulation of blood volume in utero. In: Hanson MA, Spencer JAD, Rodeck CH eds. *Fetus and Neonate, Physiology and clinical applications. Vol 1. The Circulation.* Cambridge: Cambridge University Press, 1993; 75–99
9. Bradley EC, Barr JW. Determination of blood volume using indocyanine green (Cardio-Green) dye. *Life Sci* 1968; **7**: 1001–7
10. Busse MW, Zisowsky S, Henschen S, Panning B, Piepenbrock S. Plasma volume estimation using indocyanine green. *Anaesthesia* 1993; **48**. 41–3
11. Cavill I, Trevett D, Fisher J, Hoy T. The measurement of the total volume of red cells in man: a non-radioactive approach using biotin. *Br J Haematol* 1988; **70**: 491–3
12. Chamorro G, Rodriguez JA, Dzindzio B, Rapaport E. Effect of acute isovolemic anemia on cardiac output and estimated hepatic blood flow in the conscious dog. *Circ Res* 1973; **32**: 530–5
13. Crowell JW, Ford RG, Lewis VM. Oxygen transport in hemorrhagic shock as a function of the hematocrit ratio. *Am J Physiol* 1959; **196**: 1033–8
14. Dawson AB, Evans HM, Whipple GH. Behavior of large series of dyes introduced into the circulating blood. *Am J Physiol* 1920; **51**: 232–56
15. Dietrich KA, Conrad SA, Hebert CA, Levy GL, Romero MD. Cardiovascular and metabolic response to red blood cell transfusion in critically ill volume-resuscitated non-surgical patients. *Crit Care Med* 1990; **18**: 940–4
16. Dingley J, Foex BA, Swart M, *et al.* Blood volume determination by the carbon monoxide method using a new delivery system: Accuracy in critically ill humans and precision in an animal model *Crit Care Med* 1999 (in press)
17. Doglio GR, Pusajo JF, Egurolla MA, *et al.* Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Crit Care Med* 1991; **19**: 1037–40
18. Dreyer G, Ray W. The blood volume of mammals as determined by experiments upon rabbits, guinea-pigs and mice; and its relationship to the body weight and to the surface area expressed in a formula. *Philos Trans R Soc* 1911; **201**: 133–60
19. El-Sayed H, Goodall SR, Hainworth R Re-evaluation of Evans Blue dye dilution method of plasma volume measurement. *Clin Lab Haematol* 1995; **17**:189–94
20. Ernst E, Matrai A, Kollas L. Randomised double blind placebo controlled cross-over trial on isovolaemic haemodilution in claudication. *Clin Hemorheol* 1986; 6: 279–301
21. Farjenal J, Denis C, Chatard JC, Geyssant A. An accurate method of plasma volume measurement by direct analysis of Evans blue spectra in plasma without dye extraction: Origins of albumin-space variations during maximal exercise. *Eur J Appl Physiol* 1997; **75**: 75–82
22. Fiddian-Green RG. Goals for the resuscitation of shock. *Crit Care Med* 1993, **21**: S25–31
23. Fiddian-Green RG, Baker S. Predictive value of the stomach wall pH for complications after cardiac operations: Comparison with other monitoring. *Crit Care Med* 1987; **15**: 153–6
24. Fleck A, Hawker F, Wallace PI, Raines G, Trotter J, Ledingham I McA. Increased vascular permeability: A major cause of hypoalbuminaemia in disease and injury. *Lancet* 1985; **1**: 781–3
25. Frienkel N, Screiner GE, Athens JW. Simultaneous distribution of T-1824 and ^{131}I-labelled human serum albumin in man. *Lab Clin Invest* 1953; **32**: 138–48
26. Fukui M, Shigemi K. Determination of single and repeated red cell volumes by the indicator dilution method using carbon monoxide as the indicator. *Crit Care Med* 1989; **17**: 1199–202
27. Garski TR, Staller BJ, Hepner G, Banka VS, Finney RA. Adverse reactions after administration of indocyanine green. *JAMA* 1978; **240**: 635
28. Gathje J, Steuer RR, Nicholes KRK. Stability studies on indocyanine green dye. *J Appl Physiol* 1970; **29**. 181–5
29. Gibson JG, Evans WA. Clinical studies of the blood volume: Applications of a method employing the azo dye Evans Blue and the spectrophotometer. *Lab Clin Invest* 1937; **16**: 301–16
30. Gibson JG, Seligman AM, Peacock WK. The distribution of red cells and plasma in large and minute vessels of the normal dog determined by radioisotopes of iron and iodine. *Lab Clin Invest* 1946; **25**: 848–57
31. Gillen CM, Takamta A, Mack GW, Nadel ER. Measurement of plasma volume in rats with use of fluorescent-labelled albumin molecules. *J Appl Physiol* 1994; **76**: 485–9
32. Goldberg MA, Dunning SD, Bunn HF. The regulation of the erythropoietin gene: Evidence that the oxygen sensor is a haem protein. *Science* 1988; **242**: 1412–15
33. Goldberg MA, Glass GA, Cunningham JM, Bunn HF. The regulated expression of erythropoietin by two human hepatoma cell lines. *Proc Natl Acad Sci* 1987; **84**: 7972–6
34. Gosling P, Bascom JU, Zikria BA. Capillary leak, oedema and organ failure: Breaking the triad. *Care Crit Ill* 1996; **12**· 191–7
35. Goslinga H, Eijzenbach V, Heuvelmans JHA, Van der Laan de Vries E, Melis VMJ, Schmid-Schonbein H. Custom-tailored hemodilution with albumin and crystalloids in acute ischemic stroke. *Stroke* 1992; **23**: 181–8

36 Gray SJ, Frank H. Simultaneous determination of red cell mass and plasma volume in man with radioactive sodium chromate and chromic chloride. *Lab Clin Invest* 1953; **32**: 1000–4

37 Gregersen MI. A practical method for the determination of blood volume with the dye T-1824 *J Lab Clin Med* 1944; **29**: 1266–86

38 Gys T, Hubens A, Neels H, Lauwers LF, Peeters R. Prognostic value of gastric intramural pH in surgical intensive care patients. *Crit Care Med* 1988; **16**: 1222–4

39 Hahn PF, Hevesy G. A method for blood volume determination. *Acta Physiol Scand* 1946; **1**: 3–4

40 Haldane J, Smith JL. The mass and oxygen capacity of the blood in man. *J Physiol* 1900; **25**: 331–43

41 Haller M, Akbulut C, Brechstelbauer H, *et al.* Determination of plasma volume with indocyanine green in man. *Life Sci* 1993; **53**: 1597–604

42 Haneda K, Horiuchi T. A method for measurement of total circulating blood volume using indocyanine green. *J Exp Med* 1986; **148**: 49–56

43 Harris CE, Griffiths RD, Freestone N, Billington D, Atherton ST, Macmillan RR. Intestinal permeability in the critically ill *Intensive Care Med* 1992; **18**: 38–41

44 Hartman A, Tsuda Y, Lagreze H. Effect of hypervolaemic haemodilution on regional cerebral blood flow in patients with acute ischaemic stroke. *J Neurol* 1987; **235**: 34–8

45 Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340**: 409–17

46 Henschen S. Determination of plasma volume using indocyanine green: a short review. *J Med* 1993; **24**. 10–27

47 Hillman K, Bishop G, Bristow P. Focus on: physiology and pathophysiology of fluids and electrolytes. Fluid resuscitation. *Curr Anesth Crit Care* 1996; **7**: 187–91

48 Hoffkes HG, Ehrly AM. Optimal hematocrit in patients with intermittent claudication. Exercise induced muscle tissue oxygen pressure after stepwise isovolemic hemodilution. *Clin Hemorheol* 1992; **12**: 41–56

49 Huddleston VB. *Multisystem Organ Failure. Pathophysiology and Clinical Implications.* St Louis: Mosby Year Book, 1992

50 Hudson I, Cooke IR, Holland B, *et al.* Red cell volume and cardiac output in anaemic pre-term infants. *Clin Sci* 1990; **65**: 672–5

51 Hudson IRB, Cavill IAJ, Cooke A, *et al.* Biotin labelling of red cells in the measurement of red cell volume in preterm infants. *Pediatr Res* 1990; **28**: 199–202

52 ICSH. Standard techniques for the measurement of red-cell and plasma volume. *Br J Haematol* 1973; **25**: 801–14

53 ICSH. Recommended methods for measurement of red-cell and plasma volume. *J Nucl Med* 1980; **21**: 793–800

54 ICSH. Interpretation of measured red cell mass and plasma volume in adults: Expert panel on radionuclides of the International Council for Standardization in Haematology. *Br J Haematol* 1995; **89**: 748–56

55 Isbister JP. Blood volume, hematocrit and hemorheology: The interrelationships. *Clin Hemorheol* 1994; **14**: 305–19

56 Jaenike JR, Schreiner BF, Waterstone C. The relative volumes of distribution of ^{131}I-tagged albumin and high molecular weight dextran in normal subjects and patients with heart disease. *J Lab Clin Med* 1957; **49**: 171–81

57 Jarnum S. A modified extraction method for determination of Evans Blue. *Scand J Clin Lab Invest* 1959; **11**: 332–9

58 Jelkmann W. Erythropoietin: Structure, control of production and function *Physiol Rev* 1992; **72**: 449–89

59 Jones BG. *Estimation of Blood Volume in Clinical Management.* PhD Thesis. Cardiff: University of Wales, 1994

60 Jones JG, Holland BM, Hudson IRB, Wardrop CAJ. Total circulating red cells versus haematocrit as the primary descriptor of oxygen transport by the blood. *Br J Haematol* 1990; **76**: 288–94

61 Korosue K, Ishida K, Matsuoka H, Nagao T, Tamaki N, Matsumoto S. Clinical hemodynamic and hemorheological effect of isovolemic hemodilution in acute cerebral infarction. *Neurosurgery* 1988; **23**: 148–53

62 Lanne T, Lundvall J. Mechanisms in man for rapid refill of the circulatory system in hypovolaemia. *Acta Physiol Scand* 1992; **146**: 299–306

63 Lee J, Lee L. A density method for determining plasma and red blood cell volume. *Ann Biomed Eng* 1992; **20** : 195–204

64 Linderkamp O, Holtausen H, Seifert J. Accuracy of blood volume estimation in critically ill children using ^{125}I-labelled albumin and ^{51}Cr-labelled red cells. *Eur J Pediatr* 1977; **125**: 143–51

65 Linderkamp O, Mader T, Butenandt O. Plasma volume estimation in severely ill infants and children using a simplified Evans Blue method *Eur J Pediatr* 1977; **125**: 135–41

66 Linderkamp O, Meiselman HJ, Wu PYK, Miller FC. Blood and plasma viscosity and optimal hematocrit in the normal newborn infant. *Clin Hemorheol* 1981; **1**: 575–84

67 Lowe GDO, Lee AJ, Rumley A, Price JF, Fowkes FGR. Blood viscosity and risk of cardiovascular events: The Edinburgh Artery Study. *Br J Haematol* 1997; **96**: 168–73

68 Lucking SE, Williams TM, Chaten FC, Metz RI, Mickell JJ Dependence of oxygen consumption on oxygen delivery in children with septic shock and low oxygen extraction. *Crit Care Med* 1990; **18**: 1316–19

69 Marik PE, Sibbald WJ. Effect of stored blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; **269**: 3024–9

70 Meek WJ, Gasser HS. Blood volume: A method for its determination with data for dogs, cats and rabbits. *Am J Physiol* 1918; **47**: 302–17

71 Mink RB, Pollack MM. Effect of blood transfusion on oxygen consumption in pediatric septic shock. *Crit Care Med* 1990; **18**: 1087–91

72 Morris JA, Morgan CA, Gobuty A. Measurement of fetoplacental blood volume in the human previable fetus. *Am J Obstet Gynecol* 1974; **118**: 927–31

73 Mythen MG, Webb AR. Preoperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–9

74 Nicolaides KH, Clewell WH, Rodeck CH. Measurement of fetoplacental blood volume in erythroblastosis fetalis. *Am J Obstet Gynecol* 1987; **157**: 50–3

75 Phibbs RH, Johnson P, Tooley WH. Cardiorespiratory status of erythroblastotic newborn infants: II Blood volume, hematocrit, and serum albumin concentration in relation to hydrops fetalis. *Pediatrics* 1974; **53**: 13–23

76 Phillips HM, Holland BM, Abdel-Moiz A, *et al.* Determination of red cell mass in assessment and management of anaemic babies needing blood transfusion. *Lancet* 1986; **1**: 882–4

77 Rasmussen AT, Rasmussen GB. The volume of the blood during hibernation and other periods of the year in the woodchuck (Marmota Monax). *Am J Physiol* 1917; **44**: 132–48

78 Rowell LB. *Human Circulation: Regulation During Physical Exercise.* New York: Oxford University Press, 1986

79 Schleider M, Cutler BS, Fiddian-Green RG. Sigmoid intramural pH for prediction of ischaemic colitis during aortic surgery. *Arch Surg* 1987; **122**: 881–6

80 Schmid-Schonbein H, Goslinga H. The present state of hemodilution therapies: Potentials and limits of the most potent tool of 'clinical hemorheolgy'. *Clin Hemorheol* 1992; **12**. 883–902

81 Schultz AL. A critical comparison of the T-1824 dye and iodinated albumin methods for plasma volume measurement. *J Clin Invest* 1953; **32**: 107–12

82 Semple RE, Thomsen AET, Ball AJ. Description and evaluation of a dextran-dilution technique for the determination of plasma volume in the dog and man. *Clin Sci* 1958, **17**: 511–18

83 Sherrington CS, Copeman SM. Variations experimentally produced in the specific gravity of blood. *J Physiol* 1893; **14**: 52–96

84 Shippy CR, Appel PL, Shoemaker WC. Reliability of clinical monitoring to assess blood volume in critically ill patients. *Crit Care Med* 1984; **12**: 107–12

85 Sinclair S, James S, Singer M Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997; **315**: 909–12

86 Smith HP, Arnold HR, Whipple GH. Comparative values of Welcker, carbon monoxide and dye methods for blood volume determinations. Accurate estimation of absolute blood volume. *Am J Physiol* 1921; **56**: 336–69

87 Stewart GR, Holland BM, Wardrop CAJ, Jones JG. Plasma volume measurements using rise in [IgM] after plasma infusion in newborn infants *Early Hum Dev* 1991; **25**: 60

88 Strand T, Asplund K, Eriksson S. Randomized controlled trial of hemodilution therapy in acute ischemic stroke. *Stroke* 1984; **15**: 980–9

89 Suzuki T, Dale GI. Biotinylated erythrocytes: in vivo survival and in vitro recovery *Blood* 1987; **70**: 791–5

90 Sweetnam PM, Thomas HF, Yarnell JWG, Beswick AD, Baker IA, Elwood PC Fibrinogen, viscosity and the 10 year incidence of ischaemic heart disease. The Caerphilly and Speedwell studies. *Eur Heart J* 1996; **17**: 1814–20

91 Thomas E, Jones G, de Souza P, Wardrop C. Measuring blood volume with fluorescent-labelled hydroxyethyl starch. *Crit Care Med* 1999 (in press)

92 Tomson CRV. Physiology and pathophysiology of fluids and electrolytes. Basic principles. *Curr Anesth Crit Care* 1996; **7**. 176–81

93 Tschaikowsky K, Meisner M, Durst R, Rugheimer E. Blood volume determination using hydroxyethyl starch: A rapid and simple intravenous injection method. *Crit Care Med* 1997, **25**: 599–606

94 Tudstall-Pedoe DS. Blood doping *Clin Hemorheol* 1992; **12**· 505–9

95 Usher R, Sheppard M, Lind J The blood volume of the newborn infant and placental transfusion. *Acta Paediatr* 1963; **52**· 497–512

96 Valeri CR, Cooper AG, Pivacek LE. Limitations of measuring blood volume with iodinated ^{125}I serum albumin. *Arch Intern Med* 1973; **132**: 534–8

97 Verel D. Simultaneous measurement of plasma volume with dextran and Evans Blue: Evidence of increased permeability in edema and infection *Clin Sci* 1958; **17**: 639–46

98 Wardrop CAJ, Beattie RB, Holland BM, Jones JG, Wynn RF. Measurement of feto-placental blood volume in hemolytic disease. *Pediatr Res* 1995; **38**: 461

99 Wardrop CAJ, Holland BM, Jacobs S, Jones JG. Optimisation of the blood for oxygen transport and tissue perfusion in critical care. *Postgrad Med J* 1992; **68**: S2–6

100 Webb AR. Fluid management in intensive care—avoiding hypovolaemia *Br J Intensive Care* 1997; **7**· 59–64

101 Wynn R, Al Ismail-SA, Fisher J, et *al.* Flow cytometric determination of pre-transfusion red cell volume in fetuses and neonates requiring transfusion based on RhD^{+} dilution by transfused blood. *Br J Haematol* 1995; **89**: 620–2

102 Yao AC, Moinian M, Lind J. Distribution of blood between infant and placenta after birth. *Lancet* 1969; **2**: 871–3

British Journal of Anaesthesia **84** (2): 236–8 (2000) BJA

SHORT COMMUNICATIONS

EEG controlled rapid opioid withdrawal under general anaesthesia

M. Hensel*, S. Wolter and W. J. Kox

Department of Anaesthesiology and Intensive Care, University Hospital Charité, Schumannstr. 20/21, D-10117 Berlin, Germany

**Corresponding author*

We performed rapid opioid detoxification under propofol anaesthesia in 30 opioid addicts, using the opioid receptor antagonist naltrexone. Two strategies to obtain a sufficient depth of anaesthesia and to avoid anaesthetic overdose were evaluated. Patients were allocated randomly to one of two groups. In group 1, the effects of propofol were monitored by observing clinical signs, and in group 2, depth of anaesthesia was controlled using an EEG threshold method. Withdrawal symptoms and post-anaesthetic recovery time were assessed. All patients remained stable and no anaesthetic complications were noted. There were significant differences in the total dose of propofol given (group 1, mean 72 (SD 9) mg kg^{-1}; group 2, 63 (8) mg kg^{-1}; $P < 0.01$), duration of anaesthesia (318 (53) min *vs* 309 (42) min; $P<0.05$), duration of recovery time (49 (13) min *vs* 40 (12) min; $P<0.01$) and frequency of withdrawal symptoms between groups. In addition, the incidence of side effects was different between groups (62 *vs* 29 points on a withdrawal symptom scale; $P<0.01$). To obtain a sufficient depth of anaesthesia but to avoid inappropriately large doses of anaesthetic, we consider that EEG monitoring is valuable during rapid opioid detoxification.

Br J Anaesth 2000; **84**: 236–8

Keywords: antagonists opioid, naltrexone; anaesthesia, general; monitoring, electroencephalography; complications, opioid addiction

Accepted for publication: September 23, 1999

As treatment for opioid addiction with opioid receptor antagonists can cause increased sympathetic activity, general anaesthesia has been used to prevent autonomic activity with possible complications.[1 2] In this study, we used a detoxification treatment with the opioid receptor antagonist naltrexone and the anaesthetic agent propofol. Two strategies to obtain a sufficient depth of anaesthesia were compared to assess the benefit of EEG monitoring.

Methods and results

The study was approved by the Local Ethics Committee and informed consent was obtained from each patient. Thirty opioid addicts (11 females, 19 males) were treated. Patients were allocated randomly using sealed envelopes to one of two groups of 15 patients each (group 1=treated without EEG monitoring, group 2=treated with EEG monitoring). The groups were comparable in patient characteristics, substance abuse history and physical status.

Anaesthesia was induced with propofol 1.5–3 mg kg^{-1} and maintained with a continuous i.v. infusion at a rate of 0.1–0.35 mg kg^{-1} min^{-1}. After tracheal intubation, patients breathed spontaneously from a high flow continuous positive airway pressure (CPAP) system (CF 800 P, Dräger, Lübeck, Germany). Mechanical ventilation was used in patients whose breathing was insufficient during propofol anaesthesia (two patients in group 1, one patient in group 2). The opioid receptor antagonist naltrexone was administered into the stomach using a nasogastric tube (1.5 mg kg^{-1}). Clonidine 2 μg kg^{-1} h^{-1} was given by infusion to attenuate withdrawal symptoms.

In group 1, the following signs caused by opioid withdrawal were used to judge the patient's condition and hence the dose of propofol needed: appearance of piloerection, sweating, uncoordinated movements of the limbs, coughing, flushing, lacrimation, runny nose, tachypnoea (breathing rate >20 bpm), tachycardia (heart rate >90 beat min^{-1}), hyperthermia (body temperature >37.5°C) and hypertension (systolic arterial pressure >140 mm Hg).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

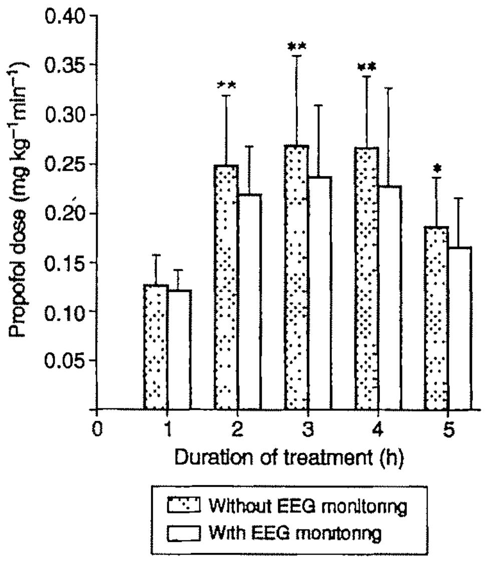


Fig 1 Amount of propofol administered during the detoxification treatment. *$P<0.05$, **$P<0.01$ between groups

In patients in group 2, EEG (Spectrum 32, Cadwell, USA) was visually analysed continuously by an experienced medical assistant. To maintain predetermined stages of depth of anaesthesia, a previously described EEG threshold method was used.[3] As the criterion of sufficiently deep anaesthesia, burst suppression of the EEG of 1–3 s ('silent seconds') was chosen. The medical assistant provided information to the anaesthetist to adjust the propofol dose. Completion of the withdrawal procedure was assessed using a previously described clinical test ('challenge test').[4] After withdrawal, patients were evaluated using a 13-item objective opioid withdrawal scale (OOWS) and a 16-item subjective opioid withdrawal scale (SOWS).[5]

Statistical analysis was carried out using the chi-square test, unpaired Student's *t* test, Mann–Whitney rank sum test or ANOVA, where appropriate. $P<0.05$ was considered statistically significant.

No anaesthetic complications were noted during the study. The amount of propofol administered during the detoxification treatment is shown in Figure 1. The total dose of propofol given to patients in group 1 (mean 72 (SD 9) mg kg^{-1}) was significantly higher than that given to patients in group 2 (63 (8) mg kg^{-1}; $P<0.01$). In patients where negligible side effects were observed ($n=9$), the total amount of propofol administered was above average (75 (4) mg kg^{-1}). Of these, eight patients (five in group 1, three in group 2) developed bradycardia (<40 beat min^{-1}) and first degree AV block, which were easily treated with atropine 0.5 mg i.v. In six patients (four in group 1, two in group 2), because of mild but persistent hypotension (systolic arterial pressure 80–90 mm Hg), 6% hydroxyethylstarch 200/0.5 was given to stabilize arterial pressure. Significantly more of these above mentioned events were seen in patients in group 1 compared with those in group 2 ($P<0.01$).

Withdrawal symptoms during the detoxification treatment were significantly greater in group 1 compared with group 2 (total number of symptoms 62 *vs.* 29; $P<0.01$). Duration of anaesthesia was 318 (53) min in group 1 compared with 309 (42) min in group 2 ($P<0.05$). Recovery time in patients in group 1 (49 (13) min) was significantly longer than that in group 2 (40 (12) min; $P<0.01$). OOWS and SOWS scores did not differ significantly between groups.

Comment

The use of the EEG to assess depth of anaesthesia is controversial.[6 7] In clinical practice, EEG monitoring often fails to predict accurately the depth of anaesthesia as the effects of both the combined use of different drugs and the nociceptive stimulation caused by surgical interventions on the EEG are not well defined.[8] Rapid opioid withdrawal during general anaesthesia is a special circumstance as nociceptive stimulation is not relevant and anaesthesia is obtained with a single agent.

In this study, visual analysis of the EEG for dose adjustment of i.v. administration of propofol was used. During opioid withdrawal, deep anaesthesia close to burst suppression is necessary to avoid sympathetic hyperactivity. Hence a threshold method using 'early' burst suppression as the index of appropriately deep anaesthesia was chosen to regulate the infusion of propofol. EEG monitoring provides an excellent tool to detect immediate short-term changes in brain activity and is more effective in adapting the dose of anaesthetic than monitoring by clinical observation alone. Using clinical criteria alone to control anaesthesia may result either in insufficient block of the sympathoadrenergic system associated with the appearance of withdrawal symptoms or in an anaesthetic overdose associated with cardiovascular side effects. EEG monitoring with a limited number of EEG leads may be clinically convenient.[9 10]

References

1 Kienbaum P, Thurauf N, Michel MC, Scherbaum N, Gastpar M, Peters J. Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after μ-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. *Anesthesiology* 1998; **88**: 1154–61

2 Hensel M, Kox WJ. Rapid opiate detoxification under general anesthesia: A new challenge for anesthesiologists and intensivists. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine.* Berlin: Springer, 1999; 646–58

3 Larsson JE, Wahlstrom G. Optimum rate of administration of propofol for induction of anaesthesia in rats. *Br J Anaesth* 1994, **73**. 692–4

4 Legarda JJ, Gossop M. A 24-h detoxification treatment for heroin addicts: a preliminary investigation. *Drug Alcohol Depend* 1994; **35**: 91–3

5 Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse* 1987; **13**: 293–308

6 Drummond JC, Brann CA, Perkins DE, Wolfe DE. A comparison of median frequency, spectral edge frequency, a frequency band power ratio, total power, and dominance shift in the determination of depth of anaesthesia. *Acta Anaesthesiol Scand* 1991; **35**: 693–9

7 Martin JT, Faulconer A, Bickford RG. Electroencephalography in anesthesiology. *Anesthesiology* 1959; **20**: 359–76

8 Rampil IJ, Laster MJ. No correlation between quantitative electroencephalographic measurements and movement response to noxious stimuli during isoflurane anesthesia in rats. *Anesthesiology* 1992; **77**: 920–5

9 Akrawi WP, Drummond JC, Kalkman CJ, Patel PM. A comparison of the electrophysiologic characteristics of EEG burst-suppression as produced by isoflurane, thiopental, etomidate, and propofol. *J Neurosurg Anesth* 1996; **8**: 40–6

10 Kuizenga K, Kalkman CJ, Hennis PJ. Quantitative electroencephalographic analysis of the biphasic concentration–effect relationship of propofol in surgical patients during extradural analgesia. *Br J Anaesth* 1998; **80**: 725–32

British Journal of Anaesthesia 84 (2) 239–41 (2000)

Use of microalbuminuria as a predictor of outcome in critically ill patients

K. L. MacKinnon[1], Z. Molnar[2], D. Lowe[3], I. D. Watson[1]* and E. Shearer[2]

[1]Department of Clinical Biochemistry, [2]Intensive Care Unit and [3]Clinical Audit Department, University Hospital Aintree, Lower Lane, Liverpool L9 7AL, UK

**Corresponding author*

We have investigated the use of microalbuminuria as a predictor of outcome in a pilot study involving 50 critically ill patients in a six-bed hospital intensive care unit (ICU). Urinary microalbumin:creatinine (M:Cr) ratios measured only 6 h after admission to the ICU demonstrated a significant difference ($P=0.01$) between survivors and non-survivors, allowing rapid identification of patients at increased risk of developing organ failure and at greater risk of death. This work suggests that earlier identification of these patients using a rapid, simple, inexpensive biochemical test is possible; if confirmed in a larger study, it may be that clinical interventions can be targeted at those most likely to benefit.

Br J Anaesth 2000; **84**: 239–41

Keywords: complications, microalbuminuria; intensive care, audit; complications, morbidity; complications, mortality

Accepted for publication: September 27, 1999

Multiple system organ failure (MSOF) has been described as the sequential failure of the lungs, liver, kidney and other vital organ systems after a variety of acute pathological conditions, such as sepsis, multiple trauma, haemorrhagic shock or pancreatitis.[1] Although the mechanisms involved in the development of this syndrome are not entirely clear, it is proposed that MSOF after trauma or surgery results from a generalized inflammatory reaction with activation of leucocytes and release of free radicals and other mediators, such as cytokines, from these cells.[2]

The optimal use of intensive care unit (ICU) resources and an accurate method of predicting the outcome of the critically ill has been the aim of many studies over several years.[3] Earlier identification of patients most at risk of serious complications and adverse outcomes would mean that they can be targeted more accurately with potentially expensive clinical interventions.

Microalbuminuria has been identified as showing promise as a predictor of outcome,[4] but requires application in a mixed population; this has been addressed in our study. Several studies have described a rapid increase in urine albumin (microalbumin) excretion in acute inflammatory conditions, which appears to be related to systemic vascular damage exemplified by capillary leak syndrome.[5 6]

The aim of our study was to assess the practicability of measurement of microalbuminuria in critically ill patients as a predictor of outcome.

Methods and results

After obtaining approval from the Hospital Ethics Committee and written informed consent from relatives, 50 patients, aged 21–79 yr (median 63 yr), were recruited after ICU admission over a 6-month period. Patients suffering from chronic organ insufficiency before this hospital admission according to APACHE II guidelines, or those with a predicted ICU stay of less than 24 h were excluded. APACHE II scores were determined 24 h after admission to the ICU. To assess the degree of organ dysfunction, a modified daily multiple organ dysfunction score (MODS) was determined.[7]

Fresh urine samples (approximately 15 ml) were collected at 6 hourly intervals from the urinary catheter and stored at 4°C until analysis of microalbumin by automated immunoturbidimetry on a Beckman Synchron CX-7. Urine creatinine was estimated on a Beckman Synchron CX-7 by a modified Jaffé rate method with alkaline picrate. Results are expressed as the microalbumin (mg):creatinine (mmol) ratio to correct for variations in urine flow rate; for the purpose of this study, a ratio of 3 mg mmol^{-1} was selected as the cut-off. Inter-assay precision was 7% for a microalbumin:creatinine (M:Cr) ratio of 7.5 mg mmol^{-1}.

Differences in variables between survivors and non-survivors were compared using the non-parametric Mann–Whitney U test with $P<0.05$ considered to be statistically

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

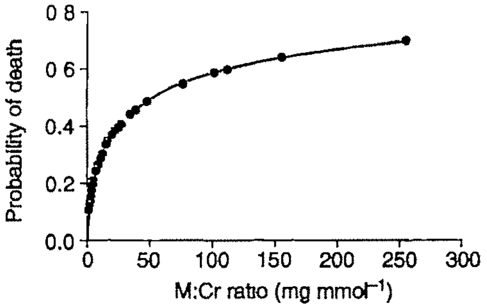


Fig 1 Predictive value of mortality obtained from the microalbumin.creatinine (M.Cr) ratio obtained 6 h after admission. Predictive values of mortality for each M:Cr ratio at 6 h were calculated using logistic regression The equation $y=1.9485+\log_{10}(M\,Cr+1)(-1\ 1389)$ was used as the transformation for M:Cr, as the resulting distribution showed considerably more symmetry. The predicted probability of death was then calculated using the equation $1/(1+e^{y})$.

significant. The relationship between M:Cr ratio and survival was also explored using multiple logistic regression (SPSS version 8.0 for Windows). Spearman rank correlation coefficients (*r*) were used to quantify the correlation between variables.

Outcome was assessed according to patient hospital survival; 36 patients survived, while 14 died. Non-survivors were slightly older as a group (median 66 yr) than survivors (median 58 yr; $P=0.12$); 36% of survivors (13 of 36) were female compared with 43% of non-survivors (six of 14). Survivors had a slightly longer median stay (6 days) in the ICU compared with non-survivors (5 days), but this was not statistically significant ($P=0.19$).

The onset of microalbuminuria was rapid, with increased urinary albumin excretion observed on admission to the ICU, with marked differences between survivors and non-survivors, even 6 h after admission. Furthermore, the degree of microalbuminuria correlated with the admission APACHE II and day 1 MODS. Spearman correlation coefficients between M:Cr after 6, 12 and 18 h with APACHE II were 0.52, 0.59 and 0.54, respectively (all $P<0.001$) and with day 1 MODS were 0.43, 0.50 and 0.46 (all $P\leq0.002$).

Logistic regression was used to model this situation using the M:Cr ratios at 6 h. The M:Cr ratio at 6 h was significantly different between survivors and non-survivors (chi-square$=5.6$, df$=1$, $P=0.02$) and the relationship between M:Cr score and the predicted probability of mortality is shown in Figure 1. This relationship changed very little for samples collected at 12 or 18 h, and therefore this curve represents the relationship between M:Cr score and the probability of mortality between 6 and 18 h. Sensitivity and specificity for 12 and 18 h were of a similar magnitude as those for 6 h; the same was also true for positive and negative predictive values (typically 50% and 85%, respectively, using a M:Cr cut-off of ≥3 mg mmol^{-1}).

Comment

In this pilot study, we examined a heterogeneous group of patients with a variety of clinical conditions, which accurately reflected patients admitted to a general ICU in the UK. This was considered advantageous, as any predictive test result must be applicable to all patients with a wide variety of diagnoses, not just small highly selected groups.

Increases in urinary albumin excretion were seen on admission to the ICU in both survivors and non-survivors and appeared to be quantitatively related to the degree of multiple organ failure, with the most microalbuminuria tending to occur in those patients with the highest APACHE II and MODS. Furthermore, the amount of microalbuminuria was significantly associated with outcome as those patients with severe microalbuminuria later died.

The simple measurement of microalbuminuria allowed rapid prediction of outcome in critically ill patients, 6 h after admission to the ICU; this is much earlier than current clinical scoring systems can be used. A high sensitivity is desirable as this selects those patients who are more likely to die and who may benefit from earlier more intensive treatment.[4 5] Calculation of the probability of death for M:Cr ratios obtained in this study (Fig. 1) suggests that a rapid indication of outcome can be obtained within 6 h of ICU admission.

In summary, the speed and magnitude of the renal permeability response to indirect injury and its association with outcome suggest that measurement of microalbuminuria may have a role in the early identification of patients at increased risk of developing MSOF, possibly leading to death. As the number of patients studied was small, further studies in larger numbers of heterogeneous patients are required to confirm this finding, validate the M:Cr cut-off and examine if measurement of microalbuminuria as an indirect measure of capillary leak may be useful as an early predictive indicator; these studies are currently underway. Confirmation of these findings means that measurement of urine microalbumin would provide a rapid, simple, inexpensive test to identify patients who may benefit from appropriate early therapeutic strategies which may prevent further capillary leak and hence the onset of MSOF and death.

Acknowledgement

Financial support for this study was from Aintree Hospitals NHS Trust. We thank the staff of the Department of Clinical Biochemistry and the ICU for their help. We also thank Dr David Wile for helpful comments during the preparation of the manuscript.

References

1 Borrelli E, Lombard PR, Grau GE, *et al.* Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Crit Care Med* 1996; **24**· 392–7

2 Gosling P, Bascom JU, Zikria BA. Capillary leak, oedema and organ failure: breaking the triad. *Care Crit Ill* 1996; **12**: 191–7

3 Chang RWS, Jacobs S, Lee B, Pace N. Predicting deaths among intensive care unit patients. *Crit Care Med* 1988; **16**: 34–42

4 Evans G, Greaves I. Microalbuminuria as a predictor of outcome. *BMJ* 1999; **318**: 207–8

5 Pallister I, Gosling P, Alpar K, Bradley S. Prediction of posttraumatic adult respiratory distress syndrome by albumin excretion rate eight hours after admission. *J Trauma* 1997; **42**: 1056–61

6 Gosling P, Shearman CP. Can we predict disease severity of acute pancreatitis? *Ann Clin Biochem* 1992; **29**: 9–10

7 Molnar Z, MacKinnon KL, Shearer E, Lowe D, Watson ID. The effect of N-acetylcysteine on total serum antioxidant potential and urinary albumin excretion in critically ill patients. *Intensive Care Med* 1998; **24**: 230–5

British Journal of Anaesthesia 84 (2): 242–4 (2000)

Do blood concentrations of neurone specific enolase and S-100β protein reflect cognitive dysfunction after abdominal surgery?

L. S. Rasmussen[1]*, M. Christiansen[2], H. Rasmussen[3], P. A. Kristensen[4], J. T. Moller[1] and the ISPOCD group[5]

[1]*Department of Anaesthesia, Centre of Head and Orthopaedics, 4132, Copenhagen University Hospital, Rigshospitalet, DK-2100, Copenhagen, Denmark.* [2]*Department of Clinical Biochemistry, Statens Serum Institut, DK-2300, Copenhagen, Denmark.* [3]*Department of Anaesthesia, Herlev Hospital, DK-2630 Herlev, Denmark.* [4]*Department of Anaesthesia, Hillerod Hospital, DK-3400 Hillerod, Denmark.*
[5]*The International Study of Postoperative Cognitive Dysfunction*

**Corresponding author*

Neurone specific enolase (NSE) and S-100β protein have been used as markers of brain damage. We hypothesized that blood concentrations of NSE and S-100β protein reflect cognitive dysfunction after abdominal surgery. We studied 65 elderly patients in whom neuropsychological testing was performed before abdominal surgery, at discharge from hospital and after 3 months. Serum concentrations of NSE and S-100β protein were measured before surgery and after 24, 48 and 72 h. Serum concentrations of S-100β protein increased significantly while NSE concentrations decreased significantly. The increase in S-100β protein concentration after 48 h was significantly greater in patients with delirium. No correlation was found between cognitive dysfunction and S-100β protein or NSE concentration. We conclude that blood concentrations of S-100β protein increase after abdominal surgery and may be related to postoperative delirium.

Br J Anaesth 2000; **84**: 242–4

Keywords: surgery, postoperative period; psychological responses, postoperative; protein, neurone specific enolase; protein, S-100β

Accepted for publication: September 2, 1999

Postoperative cognitive dysfunction (POCD) is a well known complication after cardiac surgery in elderly patients[1] and recently it has also been described after non-cardiac surgery.[2] Measurement of brain specific proteins such as neurone specific enolase (NSE) or S-100β protein in blood or cerebrospinal fluid has been described as a method of evaluating effects on the central nervous system after surgery.[3] We hypothesized that serum concentrations of NSE and S-100β protein increased after abdominal surgery in elderly patients and that the increase correlated with cognitive dysfunction.

Methods and results

The study was approved by the relevant Ethics Committees. We studied 65 patients undergoing elective major abdominal surgery, aged 60 yr or more. All gave written informed consent.

Premedication comprised diazepam 0.1–0.15 mg kg^{-1} orally. A thoracic epidural catheter was inserted and bupivacaine was given during surgery and for the following 3 days. Anaesthesia was induced with thiopental 2–5 mg kg^{-1} and fentanyl 5 μg kg^{-1}, supplemented with pancuronium 0.1 mg kg^{-1} for neuromuscular block. After orotracheal intubation, anaesthesia was maintained with 0.2–1.0% isoflurane and 50% nitrous oxide in oxygen, supplemented with bolus doses of fentanyl 1–2 μg kg^{-1}, as required.

Delirium was diagnosed based of DSM-III criteria.[4] Patients were examined every morning on the first 3 days after surgery using the orientation part of the mini-mental state examination (MMSE).[5] In addition, medical and nurse records were scrutinized.

Neuropsychological testing was performed before and after operation (after 1 week and 3 months, as reported previously).[2] Briefly, the battery comprised the following tests: MMSE[5]—as a screening test for dementia, all patients should obtain a preoperative score greater than 23 points to be included. In addition, we used the visual verbal learning test, the concept shifting test, the stroop colour word interference test and the letter–digit coding.

Normative data were available for an elderly population (control subjects) and were used to calculate z-scores for each test and to express how many standard deviations the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

patient's performance deviated from the expected in the control subjects. Patients had cognitive dysfunction when two z-scores in individual test variables or the composite z-score were above 1.96.

Serum concentrations of NSE and S-100β protein were measured before surgery and after 24, 48 and 72 h. NSE and S-100β protein were measured as described previously.[3] Serum concentrations of NSE and S-100β protein are reported as mean (range).

A Gaussian distribution of serum concentrations was obtained after logarithmic transformation. Therefore, differences between pre- and postoperative concentrations of NSE and S-100β protein, and between groups, were analysed using a *t* test. The correlation between composite z-scores and concentrations of NSE and S-100β protein was assessed using linear regression analysis. $P<0.05$ was considered statistically significant. The SAS system for Windows, v 6.12, was used for the analyses. We calculated that we would need a sample size of 50 patients. This would enable detection of a difference of 1 SD in NSE serum concentration between patients who had POCD and those who did not (a standardized difference of 1), at the 5% level of significance with 90% power. The calculation took into account that the two groups would differ in size.

We included 65 patients (49 men, 16 women), median age 68 yr (interquartile range (IQR) 65–72 yr), undergoing major abdominal surgery with a median duration of anaesthesia of 265 (IQR 225–330) min.

After operation, eight patients had delirium (12.3% (95% confidence interval (CI) 5.5–22.8%)). Thirteen patients could not be evaluated at the first postoperative neuropsychological test after a median of 8.5 (IQR 7–13) days because of patient refusal (eight patients) or severe complications (five patients). Of the remaining 52 patients, 17 (32.7% (95% CI 20.3–47.1%)) had POCD at the first postoperative test.

After 3 months, 12 of 65 patients could not be evaluated because of patient refusal or they had died. Of the remaining 53 patients, five (9.4% (95% CI 3.1–20.7%)) had POCD at follow-up testing after a median of 98 (IQR 91–102) days.

Table 1 Serum concentrations of neurone specific enolase (NSE) and S-100β protein before and after abdominal surgery (65 patients) mean (range). $^{*}P=0.002$, $^{**}P=0.01$, $^{***}P<0.0005$ compared with preoperative values

	NSE (μg litre^{-1})	S-100β protein (μg litre^{-1})
Before surgery	6.8 (2.1–27.4)	0.084 (0.01–0.80)
24 h	7.4 (1.6–76)	0.32 (0.05–1.46)***
48 h	5.6 (1.1–17.9)*	0.23 (0.02–0.98)***
72 h	5.6 (1.5–13.2)**	0.17 (0.01–0.77)***

Blood concentrations of S-100β protein and NSE are shown in Table 1. Postoperative blood concentrations of S-100β protein increased significantly at all times. From 24 to 72 h, there was a decline in values approaching the preoperative concentration. A significant decrease in NSE concentration was seen after 48 and 72 h. Because multiple statistical testing was used, we applied a Bonferroni correction but *P* values were still <0.05.

The increase in S-100β protein concentration after 48 h was significantly higher in patients who had delirium after operation ($P=0.03$) (Table 2). This was not significant when Bonferroni's correction was applied.

Regression analysis revealed no significant correlation between the degree of cognitive dysfunction expressed as the composite z-score and the change in NSE or S-100β protein at any time.

Comment

Increased concentrations of S-100β protein have been described in cardiac surgery patients but this is the first demonstration in non-cardiac surgery.[3] The increase in S-100β protein concentration after 48 h was significantly higher in patients who had delirium after operation. We found no increase in NSE concentration. No significant correlation was found between POCD and the change in NSE or S-100β protein concentration.

Postoperative cognitive disorders appearing as subtle cognitive dysfunction or delirium are common complications in elderly patients, particularly after cardiac surgery. The usefulness of biochemical markers has been assessed primarily in cardiac surgery patients and an association has been reported.[3] Cerebral complications after cardiac surgery seem to be related to cardiopulmonary bypass itself, and microembolism is probably an important factor but other embolic phenomena contribute also.[6] In our study of abdominal surgery, delirium and POCD were common but the aetiological mechanisms behind cognitive disorders after non-cardiac surgery have not been elucidated.

Peak serum concentration is probably not always the most valuable in the prediction of outcome. The early and pronounced release of S-100β protein in our study was clinically unimportant but the increase after 48 h was significantly higher in patients with delirium. There was no association between S-100β protein and performance in the

Table 2 Serum concentrations of neurone specific enolase (NSE) and S-100β protein in patients with delirium compared with those without delirium (mean (range)). After logarithmic transformation, changes in NSE and S-100β protein were compared. *P* values indicate result of unpaired *t* test

	NSE (μg litre^{-1})			S-100β protein (μg litre^{-1})		
	24 h	48 h	72 h	24 h	48 h	72 h
Delirium ($n=8$)	8.2 (3.9–10.9)	7.3 (1.9–15.3)	6.1 (2.4–9.8)	0.49 (0.16–1.46)	0.38 (0.11–0.98)	0.37 (0.07–0.77)
No delirium ($n=57$)	7.3 (1.6–76)	5.4 (1.1–17.9)	5.5 (1.5–13.2)	0.30 (0.05–1.4)	0.21 (0.02–0.71)	0.15 (0.01–0.69)
P	0.19	0.41	1.00	0.08	0.03	0.06

neuropsychological test battery. Thus release may represent only short-lasting glial cell dysfunction with no long-term clinical consequences.

In summary, blood concentrations of S-100β protein increased after abdominal surgery and may be related to postoperative delirium. Serum concentrations of neurone specific enolase did not increase after major non-cardiac surgery.

References

1 Treasure T, Smith PLC, Newman S, *et al.* Impairment of cerebral function following cardiac and other major surgery. *Eur J Cardiothorac Surg* 1989; **3**: 216–21

2 Moller JT, Cluitmans P, Rasmussen LS, *et al.* Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 1998; **351**: 857–61

3 Rasmussen LS, Christiansen M, Hansen PB, Moller JT. Do blood levels of neuron specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass? *Acta Anaesthesiol Scand* 1999; **43**: 495–500

4 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edn, revised. International version. Washington DC: American Psychiatric Association, 1987

5 Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–98

6 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994; **25**: 1393–9

British Journal of Anaesthesia 84 (2): 245–7 (2000)

Adenosine potentiation of neuromuscular blocking agents in guinea-pigs

K. Nitahara[1 3]*, P. Kornak[1], H. Nagashima[1], E. S. Vizi[1 2], F. F. Foldes[1]† and K. Dan[3]

[1]Department of Anesthesiology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, USA. [2]Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary. [3]Department of Anesthesiology, School of Medicine, Fukuoka University, Fukuoka 814-0180, Japan

**Corresponding author: Department of Anesthesiology, School of Medicine, Fukuoka University, 7-45-1, Jonan-ku, Fukuoka 814-0180, Japan*

We have investigated the effects of adenosine i.v. on neuromuscular block induced by rocuronium, vecuronium and pipecuronium in an *in vivo* guinea-pig sciatic nerve–tibialis anterior preparation. The ED_{50} of each neuromuscular blocker was determined from cumulative log dose–response regression lines (n=14). In separate experiments, adenosine 0.1 mg kg^{-1} min^{-1} or the same volume of 0.9% NaCl was given i.v. via a constant infusion and the ED_{50} of each neuromuscular blocking agent was then administered (n=24). Adenosine 0.1 mg kg^{-1} min^{-1} increased significantly maximal block induced by the ED_{50} of these neuromuscular blockers (55–72%, 49–73 % and 60–96 %, respectively, for rocuronium, vecuronium and pipecuronium; $P<0.05$). Time to maximal block after rocuronium was significantly prolonged by adenosine (1.4–2.1 min; $P<0.05$) and time to maximal block after vecuronium and pipecuronium was unchanged by adenosine. Time to maximal recovery of twitch tension after administration of the ED_{50} of all neuromuscular blocking agents was prolonged significantly by adenosine (4.5–10.7 min, 8.2–15.8 min and 47.0–128.7 min, respectively, for rocuronium, vecuronium and pipecuronium; $P<0.05$). We conclude that continuous infusion of adenosine 0.1 mg kg^{-1} min^{-1} potentiated the effects of neuromuscular blocking agents in this *in vivo* guinea-pig preparation.

Br J Anaesth 2000; **84**: 245–7

Keywords: pharmacology, adenosine; neuromuscular block, rocuronium; neuromuscular block, vecuronium; neuromuscular block, pipecuronium; guinea-pig

Accepted for publication: August 4, 1999

Adenosine and its analogues modulate synaptic transmission in a variety of tissues via the purinergic receptor (receptors for adenosine and adenine nucleotides).[1 2] At the neuromuscular junction, adenosine inhibits acetylcholine (ACh) release via the presynaptic inhibitory A_1 purinoceptor.[1 3] Segerdahl and colleagues[4] showed that continuous administration of adenosine i.v. had antinociceptive effects in patients during surgery. However, there have been no studies regarding the effects of systemically administered adenosine on the action of neuromuscular blocking agents.

To better understand the effects of systemically administered adenosine on neuromuscular blocking agents, we have investigated the effect of adenosine on neuromuscular block induced by different neuromuscular blocking agents, using an *in vivo* guinea-pig preparation. Previous work has shown that the potencies and time courses of neuromuscular effect of neuromuscular blocking agents in guinea-pigs and humans are similar.[5]

Methods and results

After obtaining approval from the Institutional Animal Care and Use Committee, 38 male guinea-pigs, weighing 300–500 g, were anaesthetized with pentobarbital and urethane i.p. The animals underwent tracheotomy and the lungs were ventilated with oxygen. Both jugular veins and one carotid artery were cannulated for injection of drugs and monitoring of arterial pressure and heart rate, respectively. Both sciatic nerves were isolated in the gluteal region, placed on bipolar platinum electrodes and crushed with a heavy ligature proximal to the electrode. The distal tendon of both tibialis anterior muscles was dissected, separated from its insertion and attached to FT03 transducers. Both sciatic nerves were stimulated with supramaximal square wave impulses of 0.2 ms duration at 0.1 Hz and the force of contraction of both tibialis anterior muscles was recorded continuously

---

†Deceased

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Influence of adenosine on the potency and time course of the effect of neuromuscular blocking drugs (mean (SEM) of four experiments). $^*P<0.05$ control *vs* adenosine group

	Control			**Adenosine 0.1 mg kg^{-1} min^{-1}**		
	Rocuronium	**Vecuronium**	**Pipecuronium**	**Rocuronium**	**Vecuronium**	**Pipecuronium**
Dose (µg kg^{-1})	64	7	4	64	7	4
Maximal block (%)	55 (6.0)	49 (4.6)	60 (8.2)	72 (7.1)*	73 (6.8)*	96 (1.9)*
Time to maximal block (min)	1.4 (0.17)	2.4 (0.28)	7.0 (1.15)	2.1 (0.15)*	3.5 (0.43)	5.0 (0.76)
Maximal recovery (% of control)	98 (1.6)	100 (0.0)	90 (1.2)	100 (0.0)	96 (1.6)	83 (3.8)
Time to maximal recovery (min)	4.5 (0.38)	8.2 (0.88)	47.0 (4.98)	10.7 (1.08)*	15.8 (1.97)*	128.7 (10.99)*

When twitch tension became stable, the ED_{50} of each neuromuscular blocking agent was determined in 14 guinea-pigs from cumulative log dose–response regression lines. The initial dose was 40 µg kg^{-1}, 5 µg kg^{-1} and 3 µg kg^{-1} in the rocuronium ($n=6$), vecuronium ($n=4$) and pipecuronium ($n=4$) groups, respectively. The subsequent incremental dose was 20 µg kg^{-1}, 2 µg kg^{-1} and 1 µg kg^{-1} in the rocuronium, vecuronium and pipecuronium groups, respectively. Each incremental dose was administered after three consecutive unchanged twitch responses were obtained after the previous dose of drug; additional doses were not given when at least 95% depression of twitch height occurred. Cumulative doses of each drug and neuromuscular responses were transformed to log-dose and probit-response values. ED_{50} values were derived from least square linear regression analysis.

The interaction of adenosine and the neuromuscular blocking agents was studied in the other 24 guinea-pigs. Adenosine 0.1 mg kg^{-1} min^{-1} or the same volume of 0.9% NaCl (control) was administered via a constant i.v. infusion throughout the experiment and the ED_{50} of rocuronium, vecuronium or pipecuronium was given as a single i.v. dose ($n=4$ per group). After administration of each neuromuscular blocking agent, maximal block of twitch tension, time to maximal block, maximal recovery of twitch tension and time to maximal recovery were recorded.

Data were analysed using the unpaired Student's *t* test and significance was assumed when $P<0.05$. Data are presented as mean (SEM).

The ED_{50} of each neuromuscular blocking agent was 64 (8.7) µg kg^{-1} for rocuronium, 7 (1.9) µg kg^{-1} for vecuronium and 4 (0.7) µg kg^{-1} for pipecuronium.

Table 1 summarizes the effects of adenosine on the neuromuscular blocking agents. Continuous infusion of adenosine 0.1 mg kg^{-1} min^{-1} alone had no effect on the height of the twitches, but significantly increased the maximal block of twitch tension induced by all blocking agents ($P<0.05$). Time to maximal block after vecuronium and pipecuronium was unchanged by adenosine, but after rocuronium, it was significantly prolonged by adenosine ($P<0.05$). Time to maximal recovery of twitch tension after all neuromuscular blocking agents was significantly prolonged by adenosine ($P<0.05$).

Comment

We investigated the effects of adenosine on three neuromuscular blocking agents used commonly in clinical practice on a guinea-pig *in vivo* sciatic nerve–tibialis anterior preparation.

Adenosine increased maximal block and prolonged the duration of block induced by all of the neuromuscular blocking agents. *In vitro* studies using mouse hemidiaphragm[1] and frog sartorius muscle[3] revealed that adenosine potentiated the effects of neuromuscular blocking agents by inhibiting ACh release via a presynaptic inhibitory A_1 purinoceptor. Therefore, it seems likely that potentiation of neuromuscular blocking agents in our study was caused by A_1 receptor mediated inhibition of ACh release.

Time to maximal block after rocuronium was prolonged and that after vecuronium and pipecuronium was unchanged by adenosine. The explanation of this finding is that the pharmacokinetic effects of adenosine (haemodynamic depressant effect, that is increase in the time of delivery of neuromuscular blocking agent) affected the onset time of rocuronium as it has the fastest baseline onset time. In a study of magnesium sulphate, potentiation of the neuromuscular blocking effects of blockers with shorter baseline onset times was less affected by magnesium sulphate.[6] Although it was not statistically significant, adenosine shortened the time to maximal block after pipecuronium. As pipecuronium has the longest baseline onset time, the pharmacodynamic effects of adenosine influenced the onset time of this blocker.

While adenosine increased neuromuscular block induced by neuromuscular blocking agents, it alone had no effect on twitch tension. This could be explained by a high margin of safety of neuromuscular transmission. Adenosine inhibited twitch tension only when the margin of safety was reduced by rocuronium, vecuronium or pipecuronium. In a mouse hemidiaphragm study, it has also been reported that adenosine or its stable analogues inhibited nerve stimulation-evoked twitches only when the margin of safety was reduced by neuromuscular blocking agents or high [Mg^{2+}].[1]

In summary, adenosine potentiated the neuromuscular blocking effects induced by rocuronium, vecuronium and pipecuronium and prolonged the time to maximal block after rocuronium in the *in vivo* sciatic nerve–tibialis anterior guinea-pig preparation. This study indicates that perioperative administration of adenosine or its analogues may increase the potency of neuromuscular blocking agents. Therefore, careful monitoring of neuromuscular block is appropriate in such cases.

References

1. Nagano O, Foldes FF, Nakatsuka H, *et al.* Presynaptic A_1-purinoceptor-mediated inhibitory effect of adenosine and its stable analogues on the mouse hemidiaphragm preparation. *Naunyn Schmiedebergs Arch Pharmacol* 1992; **346**: 197–202
2. Nitahara K, Kittel A, Liang SD, Vizi ES. A_1-receptor-mediated effect of adenosine on the release of acetylcholine from the myenteric plexus; Role and localization of ecto-ATPase and 5′-nucleotidase. *Neuroscience* 1995; **67**: 159–68
3. Giniatullin RA, Scolova EM. ATP and adenosine inhibit transmitter release at the frog neuromuscular junction through distinct presynaptic receptors. *Br J Pharmacol* 1998; **124**: 839–44
4. Segerdahl M, Ekblom A, Sandelin K, Wickman M, Sollevi A. Peroperative adenosine infusion reduces the requirements for isoflurane and postoperative analgesics. *Anesth Analg* 1995; **80**: 1145–9
5. Foldes FF, Nitahara K, Kornak PH, Nagashima H. Screening of muscle relaxants intended for clinical use in guinea-pig. *Anesthesiology* 1992; **77**: A930
6. Kussman B, Shorten G, Uppington J, Comunale ME Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block. *Br J Anaesth* 1997; **79**: 122–4

British Journal of Anaesthesia **84** (2): 248–9 (2000)

Infiltration of the abdominal wall with local anaesthetic after total abdominal hysterectomy has no opioid-sparing effect

J. R. Klein[1], J. P. Heaton[1], J. P. Thompson[1], B. R. Cotton[1], A. C. Davidson[2] and G. Smith[1*]

[1]University Department of Anaesthesia and [2]Department of Obstetrics and Gynaecology, Leicester Royal Infirmary, Leicester LE1 5WW, UK

**Corresponding author*

We have measured the effect of infiltration of the deep and superficial layers of the abdominal wound on morphine consumption and pain for 48 h after operation, in 40 patients undergoing total abdominal hysterectomy, in a double-blind randomized study. Patients received wound infiltration with 0.9% normal saline 40 ml or 40 ml of 0.25% bupivacaine with epinephrine 1:200 000. There were no significant differences between groups in morphine consumption, linear analogue scores for pain at rest or on movement, nausea or sedation during the first 48 h after operation. We conclude that infiltration of the deep and superficial layers of the wound of a Pfannenstiel incision with local anaesthetic solution did not confer additional analgesia in patients undergoing major gynaecological surgery.

Br J Anaesth 2000; **84**: 248–9

Keywords: pain, postoperative; anaesthetics local, bupivacaine; surgery, gynaecological

Accepted for publication: September 10, 1999

Previous work has suggested that administration of local anaesthetics into the wound during closure of surgical operations produces significant analgesia and is associated with a reduction in postoperative analgesic requirements.[1–3] However, a recent study showed that subcutaneous wound infiltration with local anaesthetic after total abdominal hysterectomy had no effect on morphine requirements or pain scores.[4] The purpose of this study was to establish if infiltration of the deep and superficial layers of the wound of a Pfannenstiel incision with bupivacaine after total abdominal hysterectomy had an opioid-sparing effect. Outcome measures were total opioid consumption using a patient-controlled analgesia (PCA) system and 100-mm linear visual analogue scores (VAS) for pain, sedation and nausea.

Methods and results

After obtaining approval from the Local Research Ethics Committee and informed written consent, we studied 40 ASA I–II patients, aged 20–60 yr, undergoing total abdominal hysterectomy for non-malignant disease in a double-blind randomized study. A standard Pfannenstiel incision was used. Patients were excluded if they were ASA III, suffered from hepatic, cardiovascular or respiratory disease or had any contraindication to local anaesthetic drugs. All patients underwent a standard general anaesthetic comprising a sleep dose of propofol 150–200 mg followed by vecuronium 0.1 mg kg^{-1} to facilitate tracheal intubation. Anaesthesia was maintained with 1–2% isoflurane and 66% nitrous oxide in oxygen. Shortly after induction, morphine 10 mg was administered as a standard i.v. bolus to all patients together with prochlorperazine 12.5 mg.

A syringe containing 0.9% sodium chloride 40 ml (saline group) or 40 ml of 0.25% bupivacaine with epinephrine 1:200 000 (bupivacaine group) was handed to the surgeon after removal of the uterus and closure of the anterior peritoneum. The surgeon infiltrated the muscle and subcutaneous layers of the wound during the two-stage closure. In the recovery unit, patients were provided with a patient-controlled analgesia device (Abbott PCA II); this was set to deliver morphine in 1-mg boluses with a 5-min lockout. The patient, surgeon, theatre staff and acute pain team nurses responsible for follow-up of patients on PCA in the postoperative period and the ward nursing staff were blinded to group allocation.

The acute pain team nurses ensured that patients received optimum analgesia (defined as a subjective pain rating of 'no pain at rest') before the patient was returned to the ward; they were allowed to administer bolus doses of morphine up to 5 mg i.v. in the recovery room. If 5 mg was inadequate, the anaesthetist was called to administer further analgesia as required.

In the postoperative period, pain scores at rest and on movement were recorded by the patient using a 100-mm linear visual analogue score (VAS) ranging from 0=no pain to 100=worst pain imaginable at 8, 12, 24, 36 and 48 h. Movement was standardized as sitting upright from the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Mean (SD or range) patient characteristics, morphine consumption and pain scores at rest and on movement, expressed as area under the curve (AUC) in the saline and bupivacaine groups. No significant differences between groups

	Saline ($n=20$)	**Bupivacaine ($n=20$)**
Age (yr)	40.3 (32–52)	41.4 (28–51)
Weight (kg)	68.7 (12.5)	64.0 (9.9)
Height (cm)	160.6 (7.6)	164.1 (8.9)
Duration of surgery (min)	48.0 (16.3)	44.1 (15.5)
Total morphine dose (mg)	88.3 (29.0)	85.1 (31.8)
Morphine PCA 0–24 h (mg)	56.0 (17.8)	53.9 (28.0)
Morphine PCA 24–48 h (mg)	21.7 (14.5)	21.4 (17.6)
Pain at rest (AUC) (mm h)	781.9 (78.7)	947.4 (102.4)
Pain on movement (AUC) (mm h)	1183.0 (130.5)	1214.0 (150.8)

supine position. In addition, 100-mm visual analogue scores for sedation (0=wide awake to 100=very drowsy) and nausea (0=no nausea to 100=worst possible nausea) were recorded at these times.

Based on our previous studies in patients undergoing abdominal hysterectomy with the same anaesthetic technique, the study had 90% power of detecting a two-sided significant difference at the 5% level of 30 mg in morphine consumption over 48 h.

Data were analysed using SPSS version 7 for Windows. Area under the curve (AUC) of the visual analogue scores for pain at rest and on movement, sedation and nausea from 0–48 h were calculated and the mean values for AUC compared using unpaired *t* tests (two-tailed). $P<0.05$ was considered statistically significant.

The two groups were comparable in age, weight and height. There were no significant differences in any variable, including duration of surgery. In particular, there was no significant difference in morphine consumption during the first ($P=0.74$) or second ($P=0.95$) 24-h period after operation and no significant difference in pain scores at rest ($P=0.21$) or on movement ($P=0.88$) (Table 1). Also, there were no significant differences in nausea or sedation scores between groups.

Comment

In this study, infiltration of the muscle and subcutaneous layers of the wound of a Pfannenstiel incision with 0.25% bupivacaine–epinephrine 1:200 000 had no opioid-sparing effect. PCA morphine consumption in the first and second 24-h periods was almost identical in the two groups (Table 1), and there was no difference in pain scores at rest or on movement.

There are few studies examining the effects of wound infiltration of the subcutaneous and deeper layers (e.g. intrafascial or i.m.) after intra-abdominal surgery. Infiltration of the subcutaneous and intrafascial layers of the wound with 0.25% bupivacaine 50 ml reduced opioid requirements in the first 3 days after cholecystectomy.[5] Superficial wound infiltration combined with bilateral ilioinguinal nerve blocks after Caesarean section reduced postoperative pain and requirements for additional analgesics.[6] In contrast, subcutaneous infiltration of 0.5% bupivacaine alone into the wound edges had no clinically important effect on morphine consumption after Pfannenstiel incision for lower segment Caesarean section[7] and no effect after abdominal hysterectomy.[4] In the latter study, postoperative observation for a morphine-sparing effect was continued for only 6 h.

It is possible that the lack of difference between groups in this study was related to large differences in pain scores and morphine requirements between patients. Individual pain scores varied widely despite the use of PCA. Inter-individual differences in pain scores may reflect patient perception of pain, differences in opioid effect or differences in pharmacokinetics.[4] Another possibility would be that the dose or concentration of bupivacaine was inadequate. A large volume of a dilute solution (40 ml of 0.25%) was chosen to ensure spread throughout the wound layers. However, this dose is similar to that used in two other studies which showed benefit from wound infiltration,[3 5] and is towards the upper end of the recommended dose range for patients of this weight.

A more likely explanation is that pain arising from viscera and deeper peritoneal layers is of greater significance than that from cutaneous, subcutaneous and muscular layers of a wound incision. Afferents from deeper structures would be unaffected by wound infiltration.

We found that infiltrating the subcutaneous and muscular layers of a Pfannenstiel incision with local anaesthetic did not reduce PCA morphine consumption or pain scores for the first 48 h after total abdominal hysterectomy. This may be because deeper structures are responsible for much of the painful stimulus. Other methods of analgesia such as i.p. infiltration with local anaesthetics or adjuvant use of non-steroidal anti-inflammatory drugs may prove more effective alternatives.

References

1 Bays RA, Barry L, Vasilenko P. The use of bupivacaine in elective inguinal herniorrhaphy as a fast and safe technique for relief of postoperative pain. *Surg Gynecol Obstet* 1991; **173**: 433–7

2 Sinclair R, Westlander G, Cassuto J, Hedner T. Postoperative pain relief by topical lidocaine in the surgical wound of hysterectomized patients. *Acta Anaesthesiol Scand* 1996; **40**: 589–94

3 Hannibal K, Galatius H, Hansen A, Obel E, Ejlersen E. Preoperative wound infiltration with bupivacaine reduces early and late opioid requirement after hysterectomy. *Anesth Analg* 1996; **83**: 376–81

4 Cobby TF, Reid MF. Wound infiltration with local anaesthetic after abdominal hysterectomy. *Br J Anaesth* 1997; **78**: 431–2

5 Patel JM, Lanzafame RJ, Williams JS, Mullen BV, Hinshaw JR. The effect of incisional infiltration of bupivacaine hydrochloride upon pulmonary functions, atelectasis and narcotic need following elective cholecystectomy. *Surg Gynecol Obstet* 1983; **157**: 338–40

6 Ganta R, Samra SK, Maddineni VR, Furness G. Comparison of the effectiveness of bilateral ilioinguinal nerve block and wound infiltration for postoperative analgesia after Caesarean section. *Br J Anaesth* 1994; **72**: 229–30

7 Trotter TN, Hayes-Gregson P, Robinson S, Cole L, Coley S, Fell D. Wound infiltration of local anaesthetic after lower segment Caesarean section. *Anaesthesia* 1991; **46**: 404–7

British Journal of Anaesthesia 84 (2). 250–3 (2000)

Propofol decreases stimulated dopamine release in the rat nucleus accumbens by a mechanism independent of dopamine D_2, $GABA_A$ and NMDA receptors

D. Schulte[1], L. F. Callado[2], C. Davidson[2 3], P. E. M. Phillips[2 4], N. Roewer[1], J. Schulte am Esch[1] and J. A. Stamford[2*]

[1]*Department of Anaesthesiology, University Hospital Eppendorf, Hamburg, Germany.* [2]*Neurotransmission Laboratory, Academic Department of Anaesthesia and Intensive Care, St Bartholomew's and the Royal London School of Medicine and Dentistry, Royal London Hospital, Whitechapel, London E1 1BB, UK*

Present addresses: [3]*Department of Psychiatry, Duke University Medical Center, PO Box 3870, Durham, NC 27710, USA.* [4]*Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599, USA*

**Corresponding author: Anaesthetics Unit, Royal London Hospital, Whitechapel, London E1 1BB, UK*

Although propofol (2,6-di-isopropylphenol) is a popular i.v. general anaesthetic, it has been suggested to have abuse potential. As many drugs of abuse act preferentially via release of dopamine in the limbic system, we investigated the action of propofol on stimulated dopamine release in the rat nucleus accumbens. Nucleus accumbens slices were superfused (1.6 ml min^{-1}) with artificial cerebrospinal fluid at 32°C. Dopamine release was evoked by electrical stimulation (10 pulses, 0.1 ms, 10 mA, 10 Hz, every 10 min) and monitored by fast cyclic voltammetry. Propofol 100 μmol $litre^{-1}$ reduced stimulated dopamine release over the 2 h after administration, relative to Intralipid controls, to mean 30 (SEM 2)% ($P<0.01$). The dopamine D_2 receptor antagonist metoclopramide 0.3 μmol $litre^{-1}$ increased dopamine release but did not block the effect of propofol (38 (3)%). The selective $GABA_A$ antagonist bicuculline 24 μmol $litre^{-1}$ also failed to antagonize the action of propofol (45 (3)%). The NMDA receptor antagonist dextromethorphan 10 μmol $litre^{-1}$ decreased dopamine release to 57 (6)% ($P<0.01$) but failed to block the inhibitory effect of propofol (46 (6)%). Although propofol has been reported to bind to D_2, $GABA_A$ and NMDA receptors, failure of metoclopramide and bicuculline to block its effects suggests that an agonist action at D_2 or $GABA_A$ receptors does not mediate the effects of propofol on dopamine release in the rat nucleus accumbens. The lack of effect of dextromethorphan makes an NMDA receptor antagonist action unlikely.

Br J Anaesth 2000; **84**: 250–3

Keywords: anaesthetics i.v., propofol; brain, nucleus accumbens; receptors, amino acid; receptors, dopamine; rat

Accepted for publication: August 25, 1999

Propofol (2,6-di-isopropylphenol) is a popular i.v. general anaesthetic with a low incidence of nausea. Recently however evidence has begun to emerge, albeit often circumstantial, suggesting that propofol may have abuse potential.[1] Many drugs of abuse are thought to act preferentially via dopamine within the limbic system,[2] causing either the release of dopamine or mimicking its actions at the receptor level. Paradoxically, propofol has also been reported to bind to dopamine D_2 receptors (albeit relatively weakly),[3] an action reconcilable if D_2 receptor block occurs solely *presynaptically*.

We have investigated the action of propofol on evoked dopamine release in rat nucleus accumbens slices, a component of the limbic system with a large dopaminergic input from the ventral tegmental area. Dopamine release was measured in 'real time' by fast cyclic voltammetry.[4]

Methods and results

Male Wistar rats (100–150 g) were killed by cervical dislocation and the brains were removed rapidly and chilled in ice-cold artificial cerebrospinal fluid at –1 to +1°C. A 350-μm section containing the rat nucleus accumbens was cut, transferred to the chamber and held on a stainless steel grid with a nylon mesh. The slice was superfused with oxygenated artificial cerebrospinal fluid (ACSF) 1.6 ml min^{-1} at 32°C throughout the experiment.

A carbon fibre (8×50 μm) microelectrode was inserted

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

80 µm below the surface of the slice, 200 µm from a bipolar tungsten stimulating electrode (A-M Systems, Seattle, USA). Auxiliary (stainless steel wire) and reference (Ag–AgCl) electrodes were positioned at convenient locations in the slice chamber.

Dopamine release was measured using fast cyclic voltammetry (FCV) as described previously.[4] The input voltage (1.5 cycles of a triangle waveform, –1.0 to +1.4 V *vs* Ag–AgCl, 480 V s^{-1}) was applied to the potentiostat every 500 ms. A sample and hold circuit monitored current at the oxidation potential for dopamine (+ 600 mV *vs* Ag–AgCl). Its output was displayed on a chart recorder and stored on a microcomputer using CED (Cambridge Electronic Design) 'Chart' and 'Signal' software. Electrical stimulations were applied via an NL 800 constant current isolator. Dopamine release was evoked by electrical stimulation (10 pulses, 0.1 ms, 10 mA, 10 Hz every 10 min) and monitored by FCV.

After six stable consecutive dopamine release events were obtained, propofol 100 µmol $litre^{-1}$ (Zeneca) or an equivalent amount of its diluent (Intralipid; Pharmacia Laboratories) was added to the ACSF for 2 h. Some slices were pretreated with metoclopramide 0.3 µmol $litre^{-1}$ (SmithKline Beecham), bicuculline 24 µmol $litre^{-1}$ (Sigma) or dextromethorphan 10 µmol $litre^{-1}$ (RBI) from 60 min before experimentation and throughout. In separate experiments, the effect of dextromethorphan 10 µmol $litre^{-1}$ itself was investigated. Stock solutions of each drug were prepared in distilled water with the exception of propofol which was dissolved in Intralipid. Subsequent dilutions were made in ACSF.

All drug effects on dopamine release were plotted against time. The effects of the drugs were compared with the appropriate time matched points in their respective vehicle controls using the Student's *t* test.

Electrical stimulation (10 pulses, 0.1 ms, 10 mA, 10 Hz) in the rat nucleus accumbens evoked release of dopamine that was readily detected at an adjacent carbon fibre microelectrode. Figure 1A shows a typical stimulated dopamine release event.

In the absence of drugs, stimulated dopamine release decreased slightly over the course of the experiment (Fig. 1B). Propofol 100 µmol $litre^{-1}$ significantly ($P<0.01$) reduced stimulated dopamine release relative to Intralipid controls (Fig. 1B). Metoclopramide 0.3 µmol $litre^{-1}$, the dopamine D_2 receptor antagonist, significantly increased dopamine release (data not shown) but did not block the effect of propofol (Fig. 1C). As before, propofol significantly ($P<0.05$) reduced stimulated dopamine release. Bicuculline 24 µmol $litre^{-1}$, the selective $GABA_A$ antagonist, had no effect on dopamine release alone and also failed to antagonize the action of propofol (Fig. 1D).

Dextromethorphan 10 µmol $litre^{-1}$ significantly reduced dopamine release over a similar time frame to propofol (Fig. 1E). However, propofol still significantly reduced dopamine release in the presence of dextromethorphan (Fig. 1F).

Comment

Propofol has a high brain to blood concentration ratio[5] with brain concentrations of 220 µmol g^{-1} recorded in the rat for plasma propofol concentrations of 29 µmol $litre^{-1}$. We used a concentration of propofol (100 µmol $litre^{-1}$) that, while below peak brain concentrations achieved, nonetheless represented a typical brain concentration after i.v. propofol anaesthesia in the rat. It is worth remembering that propofol is highly protein bound and thus the concentration at the active site(s) may be considerably lower.

The experiments were predicated upon the hypothesis that propofol might block presynaptic D_2 receptors, increasing dopamine release and thus explaining its apparent abuse potential. We have recently demonstrated that ketamine markedly increases dopamine release in the rat nucleus accumbens.[4]

Propofol *decreased* dopamine release, an effect suggesting an *agonist* action at D_2 receptors. Certainly, propofol binds to D_2 receptors, albeit weakly.[3] However, metoclopramide did not block the propofol response at a concentration that rapidly increased dopamine release and has been shown in this laboratory to block autoreceptor stimulation. Thus propofol, at this concentration, has no detectable D_2 agonist or antagonist activity on presynaptic D_2 receptors in the rat nucleus accumbens. Furthermore, Appadu, Strange and Lambert[3] showed that propofol, at typical serum concentrations, occupies no more than 15% of D_2 dopamine receptors.

Propofol is known to potentiate GABA-mediated synaptic inhibition and this might underlie its effect on dopamine release. However, failure of bicuculline, the specific $GABA_A$ receptor antagonist, to block propofol suggests that a $GABA_A$ agonist action does not mediate the observed effects.

Propofol causes inhibition of NMDA receptors *in vitro*[6] and this may mediate the hallucinations observed after propofol anaesthesia. However, although dextromethorphan itself decreased dopamine release, it was unable to block the action of propofol at a concentration known to block NMDA-mediated responses *in vitro.*[7]

The absence of involvement of D_2, $GABA_A$ and NMDA receptors may suggest that the action of propofol is mediated via less specific mechanisms, such as calcium and sodium channels. Voltage-sensitive calcium channels can perhaps be excluded. Although propofol can block L- and T-type calcium channels,[8 9] we have shown that forebrain dopamine release is mainly under the control of N- and P/Q-type calcium channels (Phillips and Stamford, unpublished data). More likely is the involvement of sodium channels. Propofol has been shown to inhibit glutamate release evoked by 4-aminopyridine and veratridine but not by potassium.[10] It is possible that the same phenomenon may apply to dopamine release.

In summary, we found that propofol inhibited dopamine release in the rat nucleus accumbens in a manner dependent neither on D_2, $GABA_A$ nor NMDA receptors. We suggest

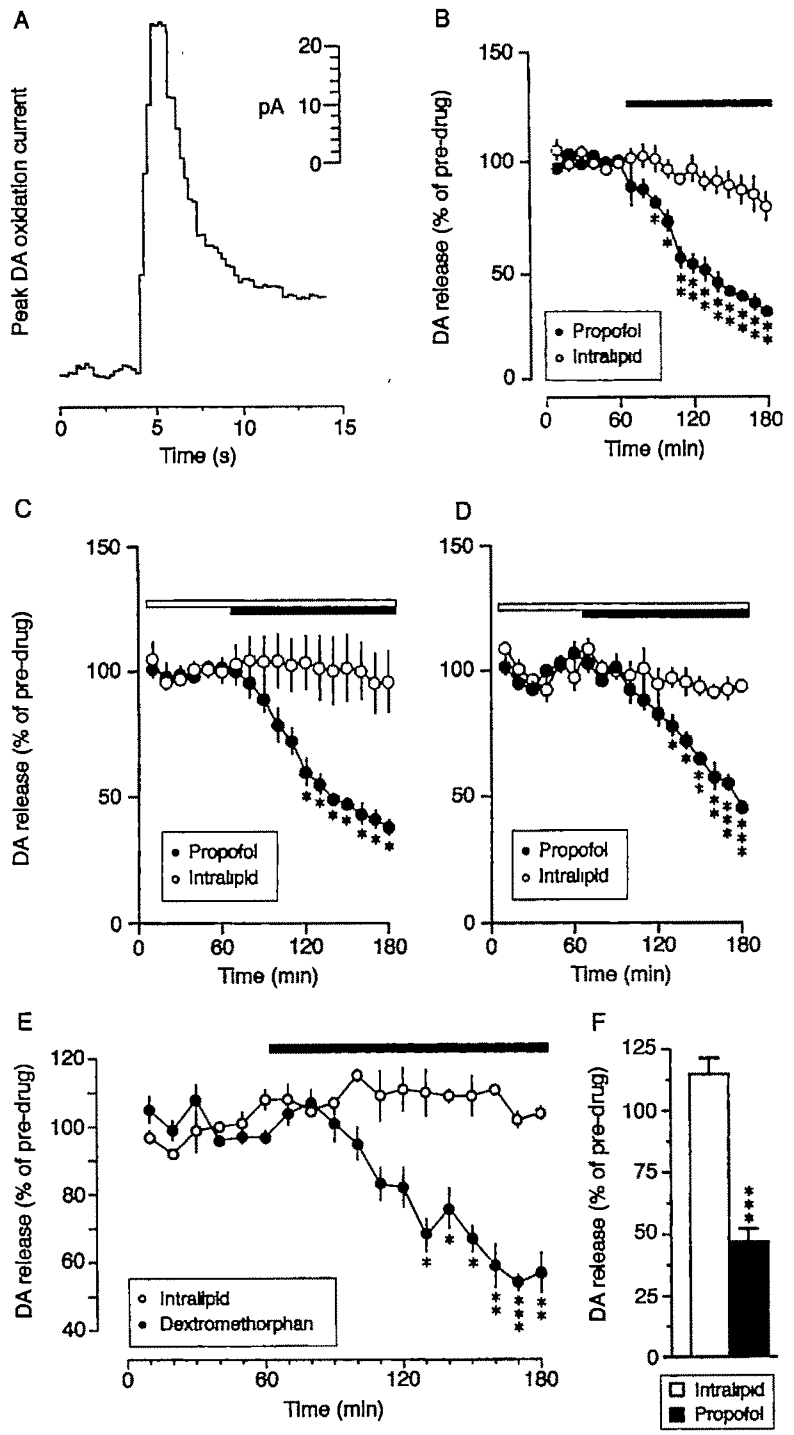


Fig 1 Propofol inhibits stimulated dopamine release. A. Sample-and-hold record of stimulated dopamine release and reuptake (as peak dopamine oxidation current) in the nucleus accumbens The period of stimulation is shown by the filled bar. B. Effect of propofol 100 μmol litre^{-1} on stimulated dopamine release in the nucleus accumbens Intralipid controls are shown for comparison. The filled bar shows the period of drug or vehicle administration. C· Effect of propofol 100 μmol litre^{-1} (filled bar) on stimulated dopamine release in the nucleus accumbens in the presence of metoclopramide 0 3 μmol litre^{-1} (open bar). Intralipid controls in the presence of metoclopramide are shown for comparison. D: Effect of propofol 100 μmol litre^{-1} (filled bar) on stimulated dopamine release in the nucleus accumbens in the presence of bicuculline 24 μmol litre^{-1} (open bar) Intralipid controls in the presence of bicuculline are shown for comparison E Effect of dextromethorphan 10 μmol litre^{-1} on stimulated dopamine release in the nucleus accumbens Intralipid controls are shown for comparison. The filled bar shows the period of drug administration. F: Effect of propofol 100 μmol litre^{-1} on stimulated dopamine release in the nucleus accumbens in the presence of dextromethorphan 10 μmol litre^{-1}, 2 h after administration. Intralipid controls in the presence of dextromethorphan are shown for comparison All values are mean (SEM), $n=4$ *$P<0.05$, **$P<0.01$, ***$P<0.001$ *vs* time-matched controls (Student's *t* test)

that propofol may be acting not through receptor mechanisms but by block of ion channels.

Acknowledgement

L. F. C. is a postdoctoral fellow supported by a grant from the Basque Government.

References

1 Zacny JP, Lichtor JL, Thompson W, Apfelbaum JL. Propofol at a subanesthetic dose may have abuse potential in healthy volunteers. *Anesth Analg* 1993; **77**: 544–52

2 DiChiara G, Imperato A. Preferential stimulation of dopamine release in the nucleus accumbens by opiates, alcohol, and barbiturates: studies with transcerebral dialysis in freely moving rats. *Ann NY Acad Sci* 1986; **373**: 367–81

3 Appadu BL, Strange PG, Lambert DG. Does propofol interact with D_2 dopamine receptors? *Anesth Analg* 1994; **79**: 1191–2

4 Hancock PJ, Stamford JA. Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. *Br J Anaesth* 1999; **82**: 603–8

5 Shyr MH, Tsai TH, Tan PP, Chen CF, Chan SH. Concentration and regional distribution of propofol in brain and spinal cord during propofol anesthesia in the rat. *Neurosci Lett* 1995; **184**: 212–15

6 Orser BA, Bertlik M, Wang LY, MacDonald JF. Inhibition by propofol (2,6 di-isopropylphenol) of the N-methyl-D-aspartate subtype of glutamate receptor in cultured hippocampal neurones. *Br J Pharmacol* 1995; **116**: 1761–8

7 Church J, Sawyer D, McLarnon JG Interactions of dextromethorphan with the N-methyl-D-aspartate receptor–channel complex: single channel recordings. *Brain Res* 1994, **666**· 189–94

8 Hirota K, Lambert DG. I.v. anaesthetic agents do not interact with the verapamil binding site on L-type voltage-sensitive Ca^{2+} channels. *Br J Anaesth* 1996; **77**: 385–6

9 Todorovic SM, Lingle CJ. Pharmacological properties of T-type Ca^{2+} current in adult rat sensory neurons. effects of anticonvulsant and anesthetic agents. *J Neurophysiol* 1998; **79**· 240–52

10 Ratnakumari L, Hemmings HC jr. Effects of propofol on sodium channel-dependent sodium influx and glutamate release in rat cerebrocortical synaptosomes. *Anesthesiology* 1997; **86**: 428–39

British Journal of Anaesthesia 84 (2) 254–6 (2000)

The intubating laryngeal mask airway does not facilitate tracheal intubation in the presence of a neck collar in simulated trauma

H. G. Wakeling* and J. Nightingale

Anaesthetic Department, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, UK
**Corresponding author: Department of Anaesthesia, Worthing Hospital, Lyndhurst Road, Worthing, East Sussex BN11 2DH, UK*

Tracheal intubation must be performed with great care in the multiply injured patient when it must be assumed that the cervical spine may be damaged. Use of conventional direct laryngoscopy usually requires removal of the neck collar and manual in-line stabilization of the head and neck. The intubating laryngeal mask (ILMA) has been designed to facilitate tracheal intubation in the neutral position. We used the ILMA to intubate the trachea in 10 patients wearing a neck collar and with cricoid pressure applied in a simulated trauma scenario. The ILMA was difficult to insert and ventilation proved difficult. In only two patients was intubation successful. These problems were probably caused by the neck collar strap under the chin lifting up and tipping the larynx anteriorly. On the basis of these findings, ILMA use in a subject wearing a neck collar cannot be recommended.

Br J Anaesth 2000; **84**: 254–6

Keywords: airway, management; equipment, masks anaesthesia; intubation, tracheal; trauma, cervical spine immobilization

Accepted for publication: September 16, 1999

After trauma, protection of the cervical spine is a vital part of patient management. Advanced trauma life support management (ATLS) requires continuous immobilization of the entire patient with a semi-rigid neck collar, tape and straps.[1] The collar remains in place until significant neck injury has been excluded. If such a patient requires tracheal intubation, the collar is usually removed and the head kept still by an assistant performing manual in-line stabilization. Adequate immobilization and collar removal can be achieved with minimal movement by a well-trained trauma team. After intubation, the collar is replaced. Even if performed carefully, this manipulation may not be ideal. The ILMA has been developed to facilitate reliable blind tracheal intubation in the neutral head position similar to the position produced by a neck collar.[2] We have investigated if the ILMA allows rapid and reliable tracheal intubation in a patient wearing a neck collar and with cricoid pressure applied in a simulated trauma scenario.

Methods and results

After obtaining approval from the Local Ethics Committee and informed written consent, we studied 10 consecutive patients undergoing anaesthesia for surgery where tracheal intubation was required. Exclusion criteria were age less than 16 yr, risk of gastro-oesophageal reflux, pre-existing head and neck abnormality, and patient refusal. A standard anaesthetic was used, including induction with propofol 2–3 mg kg^{-1} and fentanyl 1–2 μg kg^{-1} followed by atracurium 0.5 mg kg^{-1}. During the study, oxygenation and adequate depth of anaesthesia were maintained by face mask ventilation with 1–2% isoflurane and 50% nitrous oxide in oxygen.

After 2 min, one assistant performed in-line stabilization of the patient's neck. A second assistant then applied single-handed cricoid pressure and a Cormack and Lehane score was obtained by direct laryngoscopy in this position. A semi-rigid cervical collar (Stifneck Select; Laerdal Medical Corp, Wappinger's Falls, NY 12590, USA) was adjusted to the correct size and applied to the patient according to the manufacturer's instructions (Fig. 1). An appropriate size ILMA was selected (size 4 for women, size 5 for men) and inserted using the manufacturer's instructions.[3] Before insertion, the ILMA was deflated while pressing down on a firm, sterile surface into a smooth flat wedge and the tube was lubricated internally with a water-based gel. Further lubricating gel was placed on the posterior surface of the ILMA mask which was then applied to the hard palate. The ILMA was moved backwards following the curve of the rigid tube and swung down into place while being firmly applied to the palate and posterior pharyngeal wall. Cricoid pressure was released transiently to allow passage of the ILMA behind the larynx.

When in position, the cuffs were inflated (30 ml for the size 4 and 40 ml for size 5). The ILMA was connected to

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

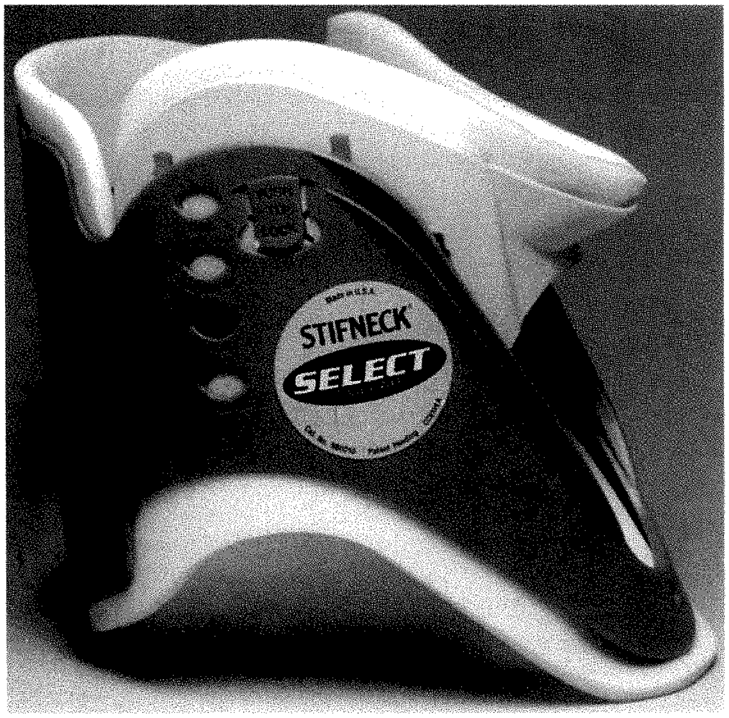


Fig 1 The Stifneck Select collar.

Table 1 Patient details, and airway and intubation data. C&L=Cormack and Lehane, Mal.=Mallampati, F=female, M=male and TMD=thyromental distance

Subject No.	Sex	Height (cm)	Weight (kg)	Age (yr)	ASA status	C&L score	Mal. score	TMD (cm)	ILMA size	Collar	Ventilation	Intubation attempts	Successful no collar
1	M	174	80	68	II	2	2	>7	5	Reg.	Good	Fail	–
2	M	168	65	24	I	3	2	>7	4	Reg.	Difficult	Fail	–
3	M	180	100	49	I	1	1	>7	5	Reg.	Difficult	Fail	Yes
4	F	158	75	40	II	2	2	>7	4	No neck	Difficult	Fail	Yes
5	M	183	80	36	II	1	1	>7	5	Reg.	Good	Fail	Yes
6	M	175	93	66	II	1	1	>7	5	Short	Good	1	–
7	F	155	77	52	II	1	2	>7	4	No neck	Good	2	–
8	M	152	74	59	II	3	2	>7	5	Reg.	Good	Fail	Yes
9	M	178	76	70	II	2	1	>7	5	Reg.	Difficult	Fail	Yes
10	F	173	80	26	II	1	1	>7	4	Short	Good	1	–

the breathing circuit and manual ventilation attempted. The handle of the ILMA was then gently adjusted to find the position giving the optimal seal. The tracheal tube (Euromedical ILM Endotracheal tube, Euromedical) was inserted into the ILMA until the 15 cm horizontal line was level with the top of the ILMA tube. The tracheal tube was advanced gently and the cuff inflated. Capnography and auscultation confirmed tracheal intubation. If the tracheal tube was not in the trachea, it was removed and the ILMA repositioned with the aim of finding the best seal before another intubation attempt was made. Up to three intubation attempts were made in any one patient before failure was recorded, the collar removed and the patient's trachea intubated by direct laryngoscopy in the first two cases or via the ILMA in subsequent cases. The study was concluded at this point and anaesthesia was continued for surgery. Whenever possible, laryngoscopy was performed by an independent observer. All ILMA insertions were performed by an experienced user (H. G. W.) with 90 previous uses (88 successfully intubated).

We intended initially to enrol 50 patients but as it became clear from the high failure rate that the ILMA was unsuitable for this purpose, we limited the study to 10 patients as we felt it was unethical to continue.

Data recorded included patient details (age, sex, height, weight, ASA grade and type of operation). In addition, Mallampati, Cormack and Lehane scores, thyromental distance, degree of difficulty with ILMA insertion, ease of ventilation and the number of intubation attempts required were recorded. In two patients, intubation was successful at the first attempt with the collar and cricoid pressure in place and in a further patient when cricoid pressure was released. In the first two patients where intubation was not achieved within three attempts, the trachea was intubated using direct laryngoscopy. In the subsequent five patients, the third ILMA intubation attempt was carried out after having removed the collar and was achieved at the first attempt in all five patients. This was to confirm that failure to intubate with the ILMA related to the collar rather than patient factors or user error. It was possible to ventilate the lungs of all 10 patients with the ILMA alone, although this was difficult in four.

Comment

The intubating laryngeal mask airway (ILMA) is an advanced form of the laryngeal mask (LMA) designed to facilitate tracheal intubation.[2] It consists of a modified LMA attached to a curved stainless steel tube. The curvature of the tube was developed using a series of sagittal magnetic resonance images (MRI) of the head and neck. The ILMA tube enables passage of an 8-mm internal diameter tracheal tube. The ILMA is designed for use in the neutral position similar to that created by wearing a semi-rigid neck collar.

Airway management in the traumatized patient involves giving special consideration to the cervical spine. Currently the ATLS advice is to immobilize the whole body on a spine board in addition to using a semi-rigid collar, tape and straps.[1] However, the collar is usually removed if tracheal intubation is required and manual in-line stabilization applied. The risk of cervical cord injury would be reduced further if removal of the collar could be avoided when securing the airway. Although the ILMA theoretically may have advantages over conventional techniques, we have shown that it did not function reliably enough to meet this expectation.

Initial insertion of the ILMA proved quite difficult because the collar restricted mouth opening. As a previous study showed a significant reduction in successful intubation when the ILMA was placed in the presence of cricoid pressure,[4] this was relaxed for ILMA insertion, but this did not improve success. When in position, it is unlikely that cricoid pressure would be compromised by the ILMA, as the tip is very similar to a laryngeal mask which does not affect the effectiveness of cricoid pressure.[5] Ventilation was difficult in 40% of immobilized patients, which compares with only 4% in a large series.[6] This was particularly worrying, as the reliability of ILMA ventilation has been an outstanding feature of the device.[6] It implies that removal of the neck collar is necessary before ILMA use in this group of patients.

Furthermore, intubation was achieved in only two patients with collars and cricoid pressure applied. A third was intubated when cricoid pressure was relaxed. The larynx appeared to be lifted up and tipped forwards by the collar when it was properly supporting the mandible, which may explain the difficulties in both ventilation and intubation. In five patients, the trachea was intubated with the ILMA at the first attempt after the collar had been removed, suggesting that the collar itself and not the user or patient factors accounted for the original failure to intubate.

Fibreoptic bronchoscopy was not used as it was not part of the original study plan and we were careful not to deviate from the approved methodology and to maintain simplicity. If the ILMA had proved to be reliable, then its use would enhance patient safety by reducing the risks involved with removing and replacing the cervical collar. As the basic technique proved to be fundamentally flawed, fibreoptic bronchoscopy, changing ILMA mask sizes or other modifications are unlikely to make it a safe technique.

In summary, the ILMA was difficult to insert, ventilation was difficult in a proportion of patients and intubation was possible in only two of 10 patients when the semi-rigid collar and cricoid pressure were in place. The ILMA cannot be recommended as an adjunct for intubation in patients wearing semi-rigid neck collars.

References

1 *Advanced Trauma Life Support. Student Manual.* Chicago: American College of Surgeons Committee on Trauma, 1997; 228
2 Brain AIJ, Verghese C, Addy EV, Kapila A. The intubating laryngeal mask I: development of a new device for intubation of the trachea. *Br J Anaesth* 1997; **79**: 699–703
3 Brain AIJ, Verghese C. *The Intubating Laryngeal Mask Airway Instruction Manual.* Maidenhead, UK: Intavent Orthofix Ltd, 1998
4 Harry RM, Nolan JP. *The Use of Cricoid Pressure with the Intubating Laryngeal Mask.* Presented at the Association of Anaesthetists of Great Britain and Ireland Annual Scientific Meeting, Glasgow, September 1998 (pages 21–22 of the meeting handbook)
5 Strang TI. Does the laryngeal mask airway compromise cricoid pressure? *Anaesthesia* 1992; **47**: 829–31
6 Baskett PJF, Parr MJA, Nolan JP. The intubating laryngeal mask. Results of a multicentre trial with experience of 500 cases. *Anaesthesia* 1998; **53**: 1174–9

British Journal of Anaesthesia **84** (**2**): 257–9 (2000)

Retrograde nasotracheal intubation with a new tracheal tube: a feasibility study

F. Agrò[1], J. Brimacombe[2]*, D. J. Doyle[3] [4], L. Marchionni[1] and R. Cataldo[1]

[1]Department of Anaesthesia, University School of Medicine Campus Biomedico, Rome, Italy. [2]Department of Anaesthesia and Intensive Care, University of Queensland, Cairns Base Hospital, The Esplanade, Cairns 4870, Australia. [3]Department of Anaesthesia, University of Toronto, Toronto, Ontario, Canada. [4]The Toronto Hospital, Toronto, Ontario, Canada

**Corresponding author*

We have assessed the feasibility of retrograde nasotracheal intubation using a flexometallic tracheal tube with a detachable pilot balloon and connector in a study of 20 consecutive adult patients undergoing oropharyngeal surgery. The technique consisted of: (1) laryngoscope-guided orotracheal intubation; (2) insertion of an 18-gauge Foley catheter through the nose and retraction into the mouth; (3) detachment of the anaesthesia circuit, pilot balloon and connector; (4) insertion of the Foley catheter tip into the proximal end of the tracheal tube and inflation of the Foley catheter cuff; (5) withdrawal of the Foley catheter and attached tracheal tube back through the nose; (6) deflation of the Foley catheter cuff; and (7) re-attachment of the pilot balloon, connector and anaesthesia circuit. The technique was successful at the first attempt in all patients. Mean time taken to insert the Foley catheter and retract it into the mouth was 19 (range 12–30) s. Mean time taken from disconnection to reconnection of the anaesthesia circuit was 8 (6–10) s. Heart rate increased after intubation, but there were no significant changes in arterial pressure. Nasal bleeding, airway problems and hypoxic events did not occur. No anatomical abnormalities or nasal trauma were detected at rhinoscopy. We conclude that retrograde nasotracheal intubation is feasible using a flexometallic tracheal tube with a detachable pilot balloon and connector.

Br J Anaesth 2000; **84**: 257–9

Keywords: equipment, Foley catheter; equipment, tubes tracheal; intubation nasotracheal, technique; surgery, oropharyngeal

Accepted for publication: August 17, 1999

Conversion of oral to nasotracheal intubation usually involves passage of a second tracheal tube through the nose and removal of the orotracheal tube. Limitations of this technique are that direct laryngoscopy is required and the airway is not protected during the exchange. We considered that retrograde nasal passage of the proximal portion of an orally placed tracheal tube might be better if a suitable tracheal tube were available. We have assessed the feasibility of retrograde nasotracheal intubation in 20 anaesthetized patients using a new flexometallic tracheal tube which has a detachable pilot balloon and connector.

Methods and results

We studied 20 consecutive adult patients requiring nasal intubation for elective oropharyngeal surgery after obtaining approval from the Ethics Committee and written informed consent. Patients were excluded if they were less than 18 yr, had a predicted or known difficult airway or had nasal pathology. The patency of each nostril was tested by asking the patient to sniff. Premedication comprised midazolam 0.04 mg kg^{-1} i.v., approximately 30 min before anaesthesia. Standard monitoring was applied, including an ECG, pulse oximeter, capnograph, non-invasive arterial pressure monitor and a peripheral nerve stimulator. Xylometazoline 0.1% vasoconstrictor nasal spray was applied to each nostril. Anaesthesia was induced with fentanyl 3 μg kg^{-1} and propofol 3 mg kg^{-1} and maintained with 1.5% isoflurane and 67% nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium 0.1 mg kg^{-1}.

Laryngoscope-guided orotracheal intubation was performed when the train-of-four count was one or less using a flexible tracheal tube with a detachable pilot balloon and connector (Agro Tube, Dar-Mallinckrodt, Modena, Italy) (Fig. 1). A size 7.5 tracheal tube was used for females and a size 8.0 for males. Two consultant

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

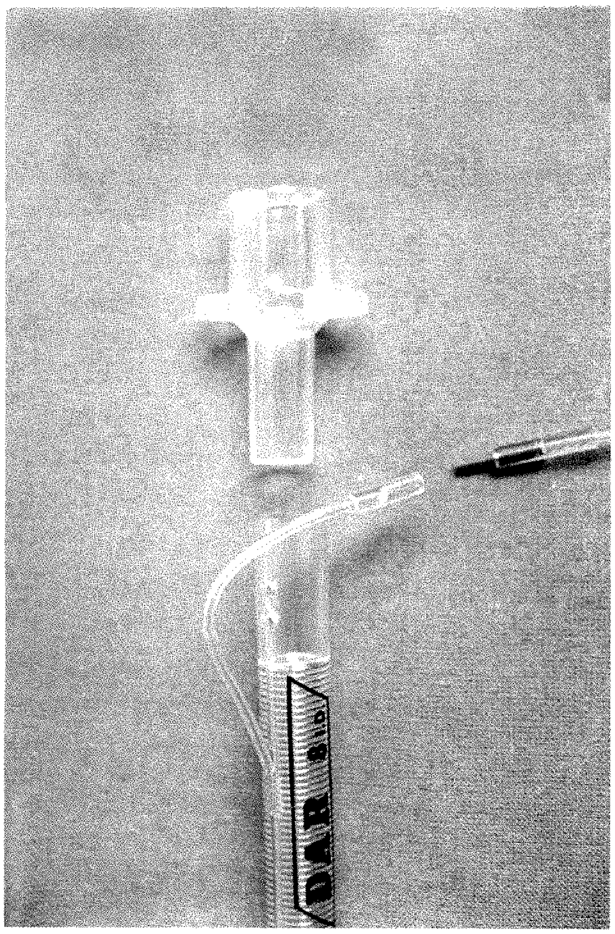


Fig 1 The proximal end of the flexible tracheal tube with detachable pilot tube and balloon.

anaesthetists who had practised the technique on manikins and cadavers before the study performed all insertions. An 18-gauge Foley catheter was inserted into the most patent nostril and retracted into the mouth using Magill's forceps. The anaesthesia circuit, pilot balloon and connector were detached from the tracheal tube. The tip of the Foley catheter was inserted into the proximal end of the tracheal tube and the Foley catheter balloon was inflated with saline to grip the inner walls of the tracheal tube. The Foley catheter was then gently withdrawn from the nose while guiding the tracheal tube into the mouth with a finger. When the tracheal tube started to emerge from the nose it was held in the oropharynx between two fingers or with Magill's forceps while it was pulled out to length. Saline was withdrawn from the balloon, the catheter removed, and the pilot balloon, connector and anaesthesia circuit re-attached. A nurse assisted with retrograde intubation by handing equipment to the anaesthetist and inflating the cuff. The anaesthetist documented any resistance felt during withdrawal of the tracheal tube through the nose. A second anaesthetist recorded: (1) the number of attempts taken to successful insertion; (2) time taken from insertion of the Foley catheter to disconnection of the anaesthesia circuit; and (3) time from disconnection to reconnection of the anaesthesia circuit.

Heart rate and arterial pressure were recorded immediately before the Foley catheter was inserted and immediately after retrograde nasal intubation was complete. Nasal bleeding, airway problems or hypoxic events (Sp_{O_2} <95%) were documented. The tracheal tube was removed at the end of surgery when the patient was awake. Bilateral rhinoscopy was performed in both nostrils before intubation and after extubation. Statistical analysis was performed using the paired *t* test. Significance was taken as $P<0.05$.

Mean age, height and weight were 42 (range 20–68) yr, 178 (168–185) cm and 75 (58–90) kg, respectively. The male:female ratio was 16:4. Intubation was successful at the first attempt in all patients. There was no resistance felt during retrograde passage of the tracheal tube. The mean time taken to insert the Foley catheter and pull it from the mouth was 19 (range 12–30) s. Mean time from disconnection to reconnection of the anaesthesia circuit was 8 (6–10) s. Duration of surgery was 97 (45–180) min. Mean heart rate increased (72 (SD 11) *vs* 81 (16) beat min^{-1}, $P=0.05$), but no significant changes were noted in systolic (120 (23) *vs* 123 (15) mm Hg) or diastolic (63 (10) *vs* 68 (10) mm Hg) arterial pressures. There were no episodes of nasal bleeding, airway problems or hypoxic events. No anatomical abnormalities or nasal trauma were detected at rhinoscopy.

Comment

We found that retrograde nasal intubation was feasible in anaesthetized patients using a tracheal tube with a detachable tube and pilot balloon. Epistaxis has been noted in 5–80%[1] and mucosal bruising in 54%[2] of nasally intubated patients. We observed no cases of epistaxis or mucosal bruising, but our small sample size means that the true incidence of these and other complications is unknown. Retrograde nasal intubation may be useful where mid-surgery conversion of oral to nasotracheal intubation is planned (e.g. major maxillofacial surgery) or might be required (e.g. malocclusion testing after molar teeth extraction). It may also be useful if conventional anterograde nasotracheal intubation has failed because an unfavourable angle of approach causes repeated impaction of the tracheal tube tip against the anterior glottis or trachea.

Possible advantages over conventional nasotracheal intubation are a lower incidence of trauma to the posterior pharyngeal wall and a lower incidence of tracheal tube obstruction caused by impaction of mucus or nasal tissues.[3] Potential disadvantages are that retrograde nasal intubation requires use of a specific tracheal tube and that accidental extubation is possible during withdrawal of the Foley catheter or while manoeuvring the tracheal tube in the oropharynx. A potential disadvantage of a detachable pilot balloon is a leak from the junction, but this was not observed.

We conclude that retrograde nasotracheal intubation is feasible using a flexometallic tracheal tube with a detachable pilot balloon and connector.

Acknowledgements

We thank Dr Federico Claro and Dr Mario Martucci for assistance with the manuscript.

References

1 O'Hanlon J, Harper KW. Epistaxis and nasotracheal intubation—prevention with vasoconstrictor spray. *Ir J Med Sci* 1994; **163**: 58–60

2 O'Connell JE, Stevenson DS, Stokes MA. Pathological changes associated with short-term nasal intubation. *Anaesthesia* 1996; **51**: 347–50

3 Cohen SP, Anderson PL. Mucoid impaction following nasal intubation in a child with an upper respiratory infection. *J Clin Anesth* 1998; **10**: 327–30

British Journal of Anaesthesia **84** **(2)**: 260–2 (2000)

BJA

CASE REPORTS

Surgery for a fractured femur and elective ICU admission at 113 yr of age†

C. D. Oliver[1], S. A. White[2]* and M. W. Platt[3]

[1]Department of Anaesthetics, Queen Elizabeth II Hospital, Welwyn Garden City, Hertfordshire AL7 4HQ, UK. [2]Neurotechnics Pain Fellow, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK. [3]Department of Anaesthetics, St Mary's Hospital, Praed Street, Paddington, London W2 1NY, UK

**Corresponding author: Department of Anaesthetics, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK*

Disability and medical dependence increase with age and as the percentage of the population over 80 yr old increases, demands on our healthcare budget will likewise grow. Clinical decision making should always balance the physiological state of the patient against the likely prognosis of the pathological state. Age may influence this decision-making process in an indirect way, as a perceived measure of physiological status, but whether age alone may be used as criteria for the type or degree of clinical intervention is a contentious point. In light of these issues, we present a woman of 113 yr, admitted to hospital with a fractured shaft of femur. The patient underwent surgery and was electively admitted to the intensive care unit for postoperative treatment. She survived surgery and several complications and was subsequently returned to the community where she celebrated her 114th birthday.

Br J Anaesth 2000; **84**: 260–2

Keywords: anaesthesia, geriatric; age factors; anaesthesia, general; intensive care

Accepted for publication: August 3, 1999

The world's elderly population (i.e. those more than 65 yr) is growing at a rate of 2.5% per year. By 2030, up to 20% of Western populations will be more than 65 yr of age. The appropriateness and priority given to surgical intervention for all patients should be based on clinical assessment of patient physiology balanced against the likely prognosis of the pathological state. Age may influence this decision-making process in an indirect way, as a perceived measure of physiological status. But whether age alone may be used as criteria for the appropriateness of clinical intervention is extremely controversial. It is against this background that we present a patient, at that time the oldest living person in the UK, who received surgery and intensive care unit (ICU) treatment at 113 yr of age and was successfully returned to the community.

Case report

A 113-yr-old woman presented to the accident and emergency department with a fractured right shaft of femur, having fallen while walking with assistance at her nursing home. Her pre-morbid history comprised partial deafness, ankle oedema and poorly documented 'intermittent confusion'. Her only regular medication was the diuretic amiloride. She was hypotensive and tachycardic, dehydrated and anaemic (haemoglobin concentration 9.8 g dl^{-1}) and apparently acutely confused. She also had a urinary tract infection. Other investigations revealed: plasma sodium 134 mmol litre^{-1}; plasma potassium 4.6 mmol litre^{-1}; plasma urea 12.2 mmol litre^{-1}; and plasma creatinine 104 μmol litre^{-1}. An electrocardiogram showed sinus rhythm, left axis deviation, partial bundle branch block and poor R wave progression. A chest x-ray was within normal limits.

There was no immediate referral for anaesthetic assessment from the admitting orthopaedic team, and the initial conservative management consisted of rehydration, blood transfusion, antibiotics and, for the fracture, traction with analgesia. On this regimen the patient was well resuscitated, yet the traction and analgesia were ultimately ineffective, failing to control the pain from the fracture site. On the eighth day of admission, the patient underwent general anaesthesia for insertion of a right femoral Rush Nail for a

---

†This article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

transverse comminuted fracture, just proximal to the knee joint. Immediately before operation (day 8), haemoglobin concentration was 10.1 g dl^{-1} and oxygen saturation on oxygen 2 litre min^{-1} was 92%. After preoxygenation, anaesthesia was induced with fentanyl 75 μg and etomidate 8 mg, with atracurium 35 mg given to facilitate tracheal intubation. The lungs were ventilated with 0.75% isoflurane and 50% nitrous oxide in oxygen. Morphine, to a total of 8 mg, was titrated against the patient's cardiovascular response and this enabled the concentration of isoflurane to be reduced.

In addition to standard anaesthetic monitoring, central venous access and pressure (CVP) monitoring were established and active external warming was undertaken. The initial CVP reading was 3 mm Hg, and with fluids this increased to 7 mm Hg by the end of the procedure. Acute atrial fibrillation was precipitated on induction to a rate of 165 beat min^{-1} with relative hypotension, at a systolic pressure of 80 mm Hg. Sinus rhythm was returned at a rate of 85 beat min^{-1} after a single bolus dose of digoxin 250 μg given over 10 min, and systolic arterial pressure accordingly increased to remain above 100 mm Hg.

Surgery lasted 90 min and was otherwise uneventful, with a measured blood loss of 600 ml over and above insensible loses. Oxygen saturation remained at 98–99% on an inspired oxygen concentration of 45%. During this period the patient received Hartmann's solution 1.5 litre, colloid 500 ml and blood 2 u. Despite elevation of the ambient theatre temperature, warming blanket and fluid warming coil, the patient's temperature was only 34.8°C at the end of the procedure.

Elective admission to the intensive care unit (ICU) then followed. The patient's trachea was extubated 5 h after operation, after which her oxygen saturation was 91–94% on air (supplementary oxygen was poorly tolerated). Haemoglobin concentration was 8.0 g dl^{-1}, improving to 12.3 g dl^{-1}, after blood transfusion of 2 u. CVP was optimized between 10 and 12 mm Hg and the patient received a total of 5693 ml of crystalloid and colloid during the 24-h ICU stay. Additional fluid was required as the core temperature returned to normal and the peripheral vasculature dilated. Urine output in this same period was 2205 ml, resulting in a positive balance of 3758 ml. The patient remained cardiovascularly stable and returned to the orthopaedic ward the next day. She remained comfortable on intermittent pethidine 25 mg i.m. (the choice of the ICU staff). This was continued for 5 days on an as required basis until oral analgesics were sufficient for pain control.

Progress on the ward was marked by two episodes of pulmonary oedema which responded promptly to diuretics. Recovery was steady and discharge occurred on day 23 after operation. She was wheelchair-bound and remained confused, but survived a further 9 months to celebrate her 114th birthday.

Discussion

Surviving the primary insult of a major fracture, let alone the subsequent surgery, at such a great age may seem unlikely, yet this patient proved very resilient and she is not alone. To our knowledge, the previous oldest recorded patient successfully undergoing general anaesthesia (for cataract extraction) was 106 yr.[1] In fact, many authors present data on elderly surgical study groups (most noticeably orthopaedic trauma) whose mean ages are in the eighth and ninth decade.[2–4] In one study, 30-day mortality rates of better than 7% increasing to only 20% at 1 yr[5] after fractured hip repair were reported. Quite clearly, it is possible to anaesthetize elderly patients successfully and return them to their pre-morbid state.

There are many factors associated with increased mortality among aged patients undergoing anaesthesia. These include pre-surgery medical problems, impaired mobility, confusional states and male sex.[4 5] Delay between trauma and surgery as a factor remains controversial,[6] as does the type of anaesthetic technique used,[4 7 8] although both regional and local anaesthesia are well tolerated among the aged.[9] Age itself is a major determinant of outcome in patients with fractured neck of femur,[5 6] but how much it influences the primary decision to proceed with surgery in the first instance cannot easily be measured. Clearly, some elderly patients may be unfit for surgery for a variety of reasons. But 'Once one is over 70 years old, one is 'more different' from others of the same age' (Professor Stanley Muravchick). Once surgery is undertaken, cardiorespiratory and thromboembolic complications are common. Long-term cognitive impairment is low (5%) and, as with cardiovascular complications, is unaffected by anaesthetic technique.[7 9]

The initial decision by the orthopaedic team was not to submit this patient for surgery because of the anticipated poor outcome. However, conservative measures were ineffective and the patient was confined to bed, in pain with no chance of survival, despite suffering from no significant life-threatening pre-trauma medical problems. Therefore, surgery and elective admission to the ICU were deemed appropriate to optimize her chance of survival. In retrospect, this patient was in a superior physiological condition to many younger patients who regularly undergo major orthopaedic surgery.

This case reflects the finding of other authors, that age alone should not be a bar to surgery.[10] However, the financial implications of an intention to treat, to whatever degree in the most senior age group will become ever greater, balanced only by the moral decision of non-intervention on an age-related basis.

References

1 Wraight WJ. The oldest patient? *Anaesthesia* 1997; **52**: 509

2 McKenzie PJ, Wishart HY, Dewar KMS, Gray I, Smith G. Comparison of spinal anaesthesia and general anaesthesia on postoperative oxygenation and perioperative mortality. *Br J Anaesth* 1980; **52**: 49–53

3 Covert CR, Fox GS. Anaesthesia for hip surgery in the elderly. *Can J Anaesth* 1989; **36**: 311–19

4 Sutcliffe AJ, Parker M. Mortality after spinal and general anaesthesia for surgical fixation of hip fractures. *Anaesthesia* 1994; **49**: 237–40

5 Davis FM, Woolner DF, Frampton C, *et al.* Prospective, multicentre trial of mortality following general or spinal anaesthesia for hip surgery in the elderly. *Br J Anaesth* 1987; **59**: 1080–8

6 Zuckerman JD, Skovron ML, Koval KJ, Aharonoff G, Frankel VH. Postoperative complications and mortality associated with operative delay in older patients who have a fracture of the hip. *J Bone Joint Surg Am* 1995; **77**: 1551–6

7 Bode RH, Lewis KP, Zarich SW, *et al.* Cardiac outcome after peripheral vascular surgery. *Anesthesiology* 1996; **84**: 3–13

8 Gianetta E, de Cian F, Cuneo S, *et al.* Hernia repair in elderly patients. *Br J Surg* 1997; **84**: 983–5

9 Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults. *JAMA* 1995; **274**: 44–50

10 Edwards AE, Seymour DG, McCarthy JM, Crumplin MKH. A 5-year study of general surgical patients aged 65 years and over. *Anaesthesia* 1996; **51**: 3–10

British Journal of Anaesthesia **84 (2)**: 263–5 (2000)

Thoracic paravertebral block: radiological evidence of contralateral spread anterior to the vertebral bodies

M. K. Karmakar[1]*, W. H. Kwok[1] and J. Kew[2]

[1]Department of Anaesthesia and Intensive Care and [2]Department of Diagnostic Radiology and Organ Imaging, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, People's Republic of China

**Corresponding author*

We report contralateral spread of contrast medium anterior to the vertebral bodies after injection of contrast through a thoracic paravertebral catheter that was used to manage pain in a patient with multiple fractured ribs. We review the literature and propose that the anatomical basis for this observation is spread in the extrapleural compartment of the thoracic paravertebral space along the subserous fascial plane.

Br J Anaesth 2000; **84**: 263–5

Keywords: anaesthetic techniques, regional, paravertebral; anatomy, paravertebral space

Accepted for publication: August 16, 1999

Thoracic paravertebral block is the technique of injection of local anaesthetic alongside the thoracic vertebra, which results in ipsilateral somatic and sympathetic nerve block, spreading to levels above and below the site of injection.[1] Contralateral anaesthesia[2–4] adjacent to the site of injection occurs in 1.1% of paravertebral injections.[5] Although the exact mechanism involved in segmental contralateral anaesthesia is still not defined, epidural spread[6] or contralateral spread anterior to the vertebrae[7] has been suggested.[8] However, the mode of contralateral spread anterior to the vertebra still remains controversial and in a recent review on thoracic paravertebral block, the authors stated that 'gross anterior spread is not possible unless the parietal pleura has been traumatized'.[9] In this report we provide radiological evidence of contralateral spread anterior to the vertebral bodies after successful thoracic paravertebral block for multiple fractured ribs and propose an anatomical basis for this mode of spread.

Case report

An 89-yr-old man, weighing 65 kg, sustained multiple fractures of his left ribs with a flail segment after a fall. His main complaints were severe left-sided chest pain, which had markedly reduced his ability to breathe deeply, cough and expectorate. Oxygen saturation was 92% with Pa_{O_2} 8.4 kPa and Pa_{CO_2} 4.4 kPa breathing room air. A chest x-ray showed fractured third to seventh ribs on the left with an associated small pleural effusion and surgical emphysema. The aortic arch was unfolded and no mediastinal shift was noted. He was referred to our pain team for pain management to facilitate respiratory care and chest physiotherapy. After informed consent, a left-sided thoracic paravertebral block was performed at the level of the fifth thoracic spine using a 16-gauge Tuohy needle (Minipack, Portex, UK), according to the technique described by Eason and Wyatt,[10] and 3 cm of an epidural catheter were inserted into the paravertebral space. After negative aspiration of the catheter for blood and CSF, a total of 20 ml of 0.5% bupivacaine with epinephrine 1:200 000 was administered over a 2-min period. The patient remained in the supine position for a further 15 min after which he reported marked pain relief. Ipsilateral anaesthesia was elicited from the second to the ninth thoracic segments, as judged by pinprick and temperature (cold), and gently springing the fractured ribs elicited no pain. No contralateral anaesthesia could be elicited and there were no significant haemodynamic changes.

To confirm the position of the catheter and demonstrate the distribution of the paravertebral injection, Iopamiro-300 10 ml (Iopamidol) diluted to 20 ml with normal saline was injected via the paravertebral catheter distal to the bacterial filter followed immediately by anteroposterior and lateral chest x-rays (Figs 1, 2). Ipsilateral spread of contrast over eight thoracic segments with contralateral spread of contrast adjacent to the sixth thoracic vertebra was also seen on the frontal chest x-ray (Fig. 1). In addition, the lateral chest x-ray also demonstrated spread of contrast onto the lateral and anterior surface of the vertebral bodies (Fig. 2) adjacent to the level of catheter placement.

Discussion

A thoracic paravertebral injection can spread to the contiguous spaces above and below, the epidural space medially

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

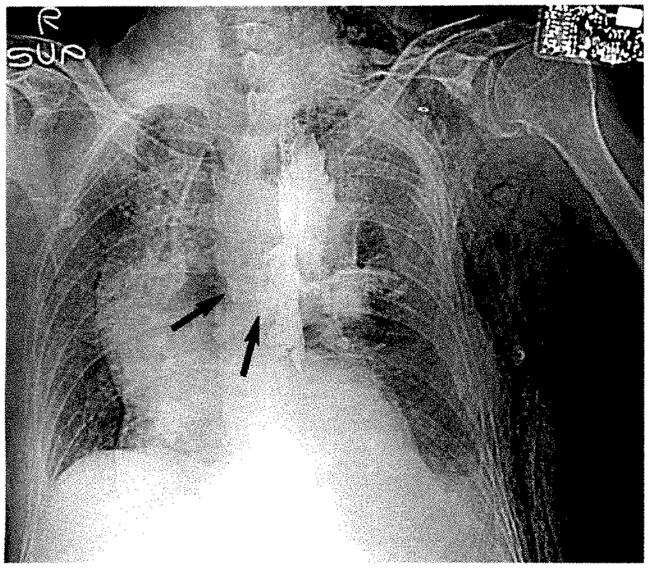


Fig 1 Chest x-ray (anteroposterior view) after injection of contrast through the paravertebral catheter. Note ipsilateral paravertebral (T2–8) and intercostal spread of contrast with arrows showing spread across the midline to the contralateral paravertebral space (T6).

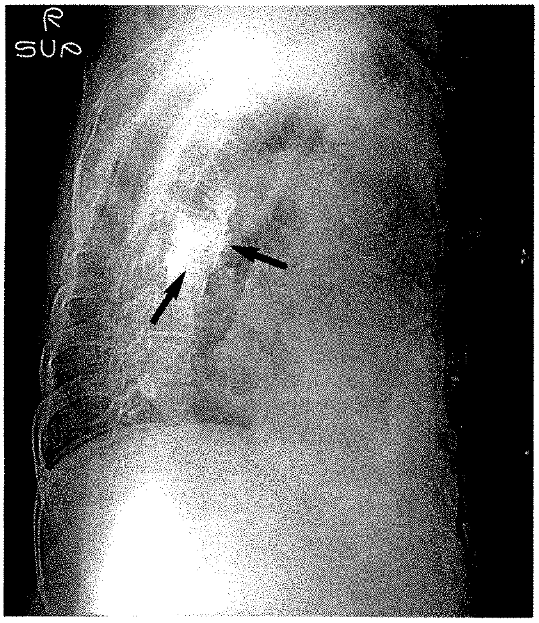


Fig 2 Chest x-ray (lateral view) after injection of contrast through the paravertebral catheter. Note paravertebral spread of contrast posterior to the vertebral bodies with arrows showing spread onto the lateral and anterior aspect of the vertebral bodies.

and the intercostal space laterally.[11] [12] This results in multiple unilateral somatic and sympathetic nerve block[1] which has been used successfully to manage pain in patients with multiple fractured ribs.[2] [10] The paravertebral injection in our patient also produced multiple unilateral intercostal nerve block which was effective in relieving pain caused by multiple fractured ribs. However, the post-contrast chest x-rays, apart from demonstrating ipsilateral paravertebral and intercostal spread, also demonstrated spread of contrast onto the lateral and anterior surface of the vertebrae with contralateral extension (Figs 1, 2). The presence of a distinct radiological pattern of contrast spread unlike interpleural injection of contrast that defines no anatomical plane[12] indicated that the injection was extrapleural in our patient. Further evidence to support extrapleural paravertebral location was the spread of contrast posterior to the vertebral bodies on the lateral chest radiograph[13] (Fig. 2).

Conacher, using the traditional method of thoracic paravertebral injection[10] in cadavers, observed that injected resin spread to the lateral surfaces of the vertebrae but in none of their dissections did the resin cross the midline.[11] However, spread across the midline of radio-opaque contrast medium in vivo[4] and coloured dye in cadavers[14] has subsequently been reported. In one of the two cases reported by Lönnqvist and Hesser[4] where contrast medium was seen to cross the midline on a frontal chest x-ray, the authors also observed two dermatomes of contralateral anaesthesia without radiological evidence of epidural extension.[4] Tenicela and Pollan described paravertebral–peridural block,[3] a modification of the traditional method of thoracic paravertebral injection, which they used to investigate the possible mechanism of contralateral anaesthesia in four fresh cadavers by injecting coloured Latex.[3] Tenicela and Pollan observed spread of Latex anteriorly from the paravertebral space to the prevertebral area in all their dissections, with frequent extension to the most anterior parts of the contralateral paravertebral space.[3] Contralateral spread of dye anterior to the vertebral bodies without evidence of interpleural spread has also been reported by Mowbray, Wong and Murray[7] after a more peripheral intercostal injection.[7] All of these reports of contralateral spread anterior to the vertebral bodies in both cadavers[3] [14] and in vivo[7] suggest that there is an extrapleural anatomical plane of communication between the intercostal spaces on either side of the thorax anterior to the vertebral bodies through the paravertebral spaces. Review of the literature shows that such an anatomical plane of communication exists.

The thoracic paravertebral space is described as a wedge-shaped space sandwiched between the head and necks of the ribs.[9] The 'endothoracic fascia',[15–18] which is the deep fascia of the thorax,[17] traverses the thoracic paravertebral space. This thin fibroelastic structure[18] is interposed between the parietal pleura and the innermost intercostal muscle in the chest wall[15–19] and between the parietal pleura anteriorly and the superior costotransverse ligament with the transverse process posteriorly in the paravertebral space.[16] Medially, the endothoracic fascia is attached to the periosteum of the vertebral bodies and becomes continuous with the prevertebral fascia that covers the vertebrae and the intervertebral discs.[17] [18] The thoracic paravertebral space is therefore divided into two potential fascial compartments by the endothoracic fascia, namely the anterior 'extrapleural' and the posterior 'subendothoracic' paravertebral compartments (Fig. 3).

In between the parietal pleura and the endothoracic fascia

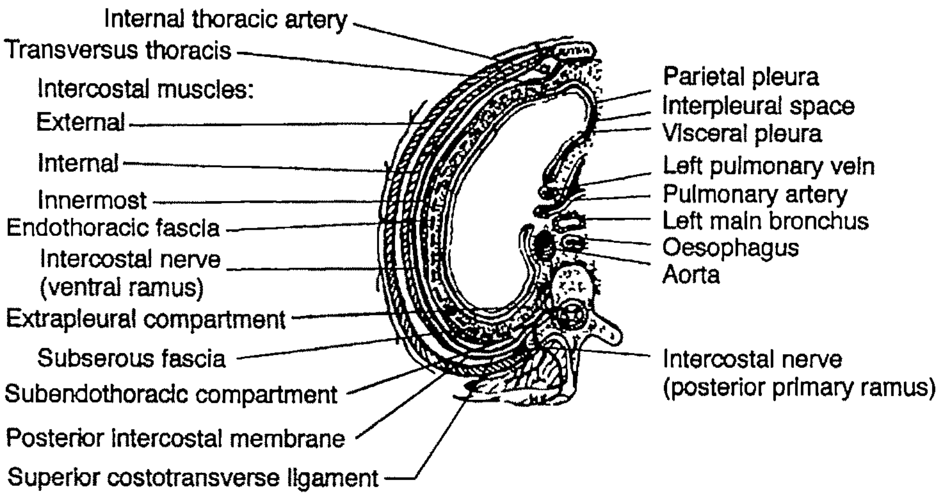


Fig 3 The subserous fascial plane and its relation to the anatomy of the thoracic paravertebral space and chest wall.

is an intervening layer of areolar connective tissue,[17–19] the 'subserous fascia',[17 19] which provides the connective tissue investment for the mediastinal structures.[17] This acts as a channel of communication for the paravertebral spaces on either side anterior to the vertebral bodies (Fig. 3). The vertebral attachment of the endothoracic fascia prevents anterior vertebral spread of contrast[19] and may prevent epidural spread after an extrapleural paravertebral injection. Based on the anatomy described, an extrapleural paravertebral compartment injection could spread to the contiguous spaces above and below, the intercostal spaces laterally and via the subserous layer of connective tissue to the anterior surface of the vertebra and on to the contralateral paravertebral space.

In summary, we have demonstrated that a thoracic paravertebral injection, apart from producing multi-dermatomal unilateral anaesthesia, can also result in contralateral paravertebral spread anterior to the vertebral bodies. We believe that the anatomical basis for this observation is spread in the extrapleural paravertebral compartment along the subserous layer of connective tissue.

References

1 Cheema SPS, Ilsley D, Richardson J, Sabanathan S. A thermographic study of paravertebral analgesia. *Anaesthesia* 1995; **50**: 118–21

2 Gilbert J, Hultman J. Thoracic paravertebral block, a method of pain control. *Acta Anaesthesiol Scand* 1989; **33**· 142–5

3 Tenicela R, Pollan SB. Paravertebral–peridural block technique: a unilateral thoracic block. *Clin J Pain* 1990; **6**: 227–34

4 Lonnqvist PA, Hesser U. Radiological and clinical distribution of thoracic paravertebral blockade in infants and children. *Paediatr Anaesth* 1993; **3**· 83–7

5 Lonnqvist PA, MacKenzie J, Soni AK, Conacher ID. Paravertebral blockade. Failure rate and complications *Anaesthesia* 1995; **50**· 813–15

6 Purcell-Jones G, Pither CE, Justins DM Paravertebral somatic nerve block: a clinical, radiographic, and computed tomographic study in chronic pain patients *Anesth Analg* 1989; **68**. 32–9

7 Mowbray A, Wong KKS, Murray JM. Intercostal catheterisation. An alternative approach to the paravertebral space. *Anaesthesia* 1987; **42**· 958–61

8 Gilbert J, Schuleman S, Sharp T. Inadvertent paravertebral block. *Anaesthesia* 1989, **44**: 527–8

9 Richardson J, Lonnqvist PA. Thoracic paravertebral block. *Br J Anaesth* 1998; **81**. 230–8

10 Eason MJ, Wyatt R. Paravertebral thoracic block–a reappraisal. *Anaesthesia* 1979; **34**. 638–42

11 Conacher ID. Resin injection of thoracic paravertebral spaces. *Br J Anaesth* 1988; **61**: 657–61

12 Conacher ID, Kokri M Postoperative paravertebral blocks for thoracic surgery. A radiological appraisal. *Br J Anaesth* 1987, **59**: 155–61

13 Johnson LR, Rocco AG, Ferrante FM. Continuous subpleural–paravertebral block in acute thoracic herpes zoster. *Anesth Analg* 1988; **67**: 1105–8

14 Lonnqvist PA, Hildingsson U. The caudal boundary of the thoracic paravertebral space. A study in human cadavers. *Anaesthesia* 1992; **47**: 1051–2

15 Williams PL, Bannister LH, Berry MM, *et al*, eds. The pleura In: *Gray's Anatomy*, 38th Edn. Edinburgh Churchill Livingstone, 1995, 1162

16 Ferner H, ed. Thorax, Abdomen and Extremities. In· Pernkopf Atlas of *Topographical* and *Applied Human Anatomy, volume II*, 2nd Edn. Translated by Monsen H. Baltimore· Urban and Schwarzenberg, 1980; 17 & 123–9

17 Dugan DJ, Samson PC. Surgical significance of the endothoracic fascia. The anatomic basis for empyemectomy and other extrapleural technics *Am J Surg* 1975; **130**: 151–8

18 Im JG, Webb WR, Rosen A, Gamsu G Costal pleura: appearances at high-resolution CT. *Radiology* 1989; **171** 125–31

19 Moore DC, Bush WH, Scurlock JE Intercostal nerve block· a roentgenographic anatomic study of technique and absorption in humans *Anesth Analg* 1980, **59**. 815–25

British Journal of Anaesthesia 84 (2): 266–9 (2000)

BJA

COMMENTARY

Self-citations in six anaesthesia journals and their significance in determining the impact factor

A. Fassoulaki*, A. Paraskeva, K. Papilas and G. Karabinis

Department of Anaesthesia, St Savas Hospital, 171 Alexandra's Ave, 11522 Athens, Greece
**Corresponding author: 57–59 Raftopoulou Street, 11744 Athens, Greece*

Self-citation of a journal may affect its impact factor. We investigated self-citations in the 1995 and 1996 issues of six anaesthesia journals by calculating the self-citing and self-cited rates for each journal. Self-citing rate relates a journal's self-citations to its total number of references. We defined self-cited rate as the ratio of a journal's self-citations to the number of times it is cited by the six anaesthesia journals. We also correlated self-citing rates with the impact factor of the six journals for 1997. Citations among the six journals differed significantly ($P<0.0001$). *Anesthesiology* had the highest self-citing rate (57%). *Anaesthesia, Anesthesia and Analgesia, British Journal of Anaesthesia, Canadian Journal of Anaesthesia* and the *European Journal of Anaesthesiology* had self-citing rates of 28%, 28%, 30%, 11% and 4% respectively. The self-cited rates were 31%, 35%, 34%, 27%, 31% and 17% for *Anaesthesia, Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Canadian Journal of Anaesthesia* and the *European Journal of Anaesthesiology*, respectively. North America journals cited the North America literature. This also occurred, to a lesser extent, in the European anaesthesia journals. A significant correlation between self-citing rates and impact factors was found ($r=0.899$, $P=0.015$). A high self-citing rate of a journal may positively affect its impact factor.

Br J Anaesth 2000; **84**: 266–9

Keywords: anaesthesia, journals; publications, impact factor; publications, anaesthesia

Accepted for publication: September 24, 1999

The impact factor of a journal represents the frequency with which its articles have been cited for a given period of time. It is calculated by dividing the number of all current citations of source items from a journal during the previous 2 yr by the number of articles published in that journal during those 2 yr.[1 2] However, the frequency of self-citations of a journal may affect its impact factor.

In this study, we have investigated the self-citation frequency of six anaesthesia journals and its possible effect on their impact factors.

Methods

Self-citations during 1995 and 1996 were investigated in six anaesthesia journals: *Anaesthesia, Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Canadian Journal of Anaesthesia* and *European Journal of Anaesthesiology*. Abstracts, supplement issues, letters and editorials were excluded.

We calculated the self-citing rate, which relates a journal's self-citations to its total number of references.[1] For example, the journal *Anesthesiology* made references to 7157 items, including 4074 of its own articles. Its self-citing rate is 4074/7157=57%.

The self-citing rates of the six anaesthesia journals in 1995 and 1996 were correlated with their impact factors for the year 1997, taken from the SCI of Journal Citation Report.[1] These impact factors were: 1.489, 4.625, 2.830, 2.241, 1.316 and 0.914 for *Anaesthesia, Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Canadian Journal of Anaesthesia* and *European Journal of Anaesthesiology*, respectively.

We also calculated the self-cited rate for the six anaesthesia journals, that is the ratio of a journal's self-citations to the number of times it is cited by the six anaesthesia journals, including itself.[1] For example, during the 2-yr period, *Anesthesiology* was cited 11 540 times by all six journals, including 4074 times it cited itself. Its self-cited rate is 4074/11540 or 35%. As we only included the six anaesthesia journals, the calculated self-cited rate differs from the standard definition derived from the Institute for

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

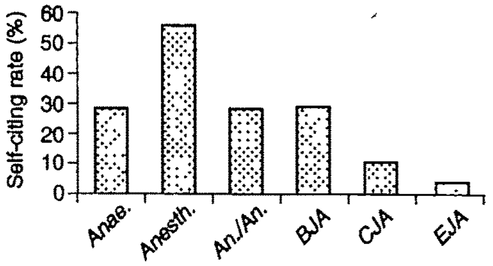


Fig 1 Self-citing rates (%) of *Anaesthesia* (*Anae*.), *Anesthesiology* (*Anesth*.), *Anesthesia and Analgesia* (*An*./*An*.), *British Journal of Anaesthesia* (*BJA*), *Canadian Journal of Anaesthesia* (*CJA*) and *European Journal of Anaesthesiology* (*EJA*) for 1995 and 1996

Scientific Information (ISI). The ISI defines self-cited rate as the ratio of journal self-citations to the number of times it is cited by all other journals, including itself.[1]

Statistical analysis

Statistical analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences) 8.0. The citations attributed to each journal by the other five journals were compared among the six journals using the chi-square test. To identify the contribution of different cells to the significance of this chi-square, we used adjusted standardized residuals. The adjusted standardized residuals followed the t distribution. For standardized residuals >1.96, $P<0.05$ and for standardized residuals >2.56, $P<0.01$. Spearman's rank (r_s) correlation coefficient was used to assess the correlation between the self-citing rates of the journals and their impact factors.

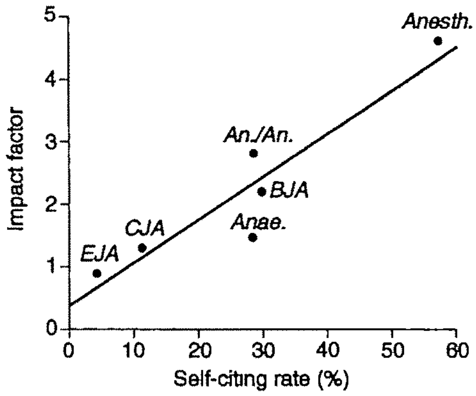


Fig 2 Correlation between self-citing rates and impact factors of the six anaesthesia journals (*Anaesthesia* (*Anae*.), *Anesthesiology* (*Anesth*.), *Anesthesia and Analgesia* (*An*./*An*.), *British Journal of Anaesthesia* (*BJA*), *Canadian Journal of Anaesthesia* (*CJA*) and *European Journal of Anaesthesiology* (*EJA*)).

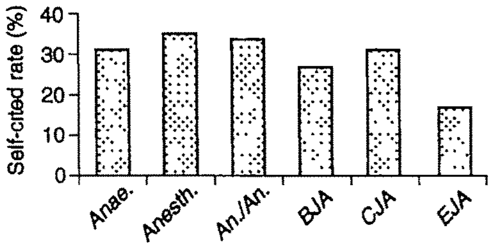


Fig 3 Self-cited rates of *Anaesthesia* (*Anae*.), *Anesthesiology* (*Anesth*.), *Anesthesia and Analgesia* (*An*./*An*.), *British Journal of Anaesthesia* (*BJA*), *Canadian Journal of Anaesthesia* (*CJA*) and *European Journal of Anaesthesiology* (*EJA*) for 1995 and 1996.

Results

The total number of publications investigated in the six anaesthesia journals for the years 1995 and 1996 was 3144. The total number of citations was 27 683. *Anesthesiology* had the highest self-citing rate. *Anaesthesia*, *Anesthesia and Analgesia* and *British Journal of Anaesthesia* followed with similar self-citing rates (28%, 28% and 30%, respectively). The *Canadian Journal of Anaesthesia* and *European Journal of Anaesthesiology* had much lower self-citing rates (11% and 4%, respectively) (Fig. 1). There was a significant correlation between self-citing rates and impact factors for the six anaesthesia journals ($r=0.899$, $P=0.015$) (Fig. 2).

Individual comparisons showed that *Anaesthesia* favoured itself, the *British Journal of Anaesthesia* and the *European Journal of Anaesthesiology* (adjusted residuals 33.7, 12.9 and 3.6, respectively), but had no significant effect on the *Canadian Journal of Anaesthesia*, and a negative effect on *Anesthesiology* and *Anesthesia and Analgesia*. *Anesthesiology* favoured itself (adjusted residual 30.4), was indifferent to *Anesthesia and Analgesia* and had a negative impact on the remaining four journals. *Anesthesia and Analgesia* favoured itself and *Anesthesiology* and had a negative effect on the three European journals, *Anaesthesia*, *British Journal of Anaesthesia* and the *European Journal of Anaesthesiology*. The *British Journal of Anaesthesia* showed similar behaviour as *Anaesthesia*. It favoured itself (adjusted standardized residual 21.2) and the *European Journal of Anaesthesiology*, and had a negative impact on *Anesthesiology*, *Anesthesia and Analgesia* and the *Canadian Journal of Anaesthesia*. The *European Journal of Anaesthesiology* favoured itself, *Anaesthesia* and the *British Journal of Anaesthesia*. It had a negative impact regarding the citations it gave to *Anesthesiology* and *Anesthesia and Analgesia* and had no effect on the *Canadian Journal of Anaesthesia*.

The self-cited rates for *Anaesthesia*, *Anesthesiology*, *Anesthesia and Analgesia*, *British Journal of Anaesthesia*, *Canadian Journal of Anaesthesia* and *European Journal of Anaesthesiology* were 31%, 35%, 34%, 27%, 30% and 17%, respectively (Fig. 3).

The citations each journal gave to other journals, including itself, and the citations each journal received from the other journals differed significantly among the six journals (chi-square=3526, df=23, $P<0.0001$) (Table 1).

Table 1 Citations each journal gave to other journals, including itself (rows), and the citations each journal received from the other journals (columns) (*Anaesthesia* (*Anae*), *Anesthesiology* (*Anesth.*), *Anesthesia and Analgesia* (*An/An*), *British Journal of Anaesthesia* (*BJA*), *Canadian Journal of Anaesthesia* (*CJA*) and *European Journal of Anaesthesiology* (*EJA*)) Chi-square=3526,12, df=23, $P<0.0001$ For adjusted residuals ≥ 1.96, $P<0.05$

	Anae.	*Anesth.*	*An./An.*	*BJA*	*CJA*	*EJA*	Total
Anae	962	803	487	909	156	64	3381
Citations							
Adjusted residual	33.7	−22.6	−11.5	12.9	−0.9	3.6	
Anesth							
Citations	351	4074	1535	910	233	54	7157
Adjusted residual	−19.8	30.4	−1.6	−15.2	−7.6	−4.3	
An./An.							
Citations	613	3252	2110	1055	316	59	7405
Adjusted residuals	−9.5	4.5	15.5	−11.6	−3.0	−4.0	
BJA							
Citations	559	1654	873	1412	179	80	4757
Adjusted residual	1.1	−10.6	−6.9	21.2	−4.1	3.0	
CJA							
Citations	412	1336	905	588	418	28	3687
Adjusted residual	−0.2	−7.2	3.8	−4.7	19.4	−2.8	
EJA							
Citations	225	421	210	321	60	59	1296
Adjusted residual	7.1	−6.9	−5.2	5.7	−0.5	11.0	
Total							
Citations	3122	11 540	6120	5195	1362	344	27 683

Discussion

All six anaesthesia journals had a self-citing rate higher than the citing rates they gave to the other journals. *Anesthesiology* favoured itself more than the other journals. This means that its self-citations may contribute to a greater extent to the number of times it was cited during the years 1995 and 1996 compared with *Anesthesia and Analgesia* or the *British Journal of Anaesthesia*. It had no positive impact on any of the other journals, including those from North America. *Anaesthesia*, *Anesthesia and Analgesia* and the *British Journal of Anaesthesia* had similar self-citing rates, which were relatively close to their self-cited rates. Thus the rate these journals were cited by all journals, including themselves, did not appear to be affected positively by their self-citations.

Overall, we may identify a mutual 'support' or at least neutral behaviour among the three European journals, *Anaesthesia*, *British Journal of Anaesthesia* and the *European Journal of Anaesthesiology*. In contrast, *Anesthesiology* exhibited a negative impact towards all other journals, except *Anesthesia and Analgesia*, to which it was indifferent, and was 'supported' only by *Anesthesia and Analgesia*. *Anesthesia and Analgesia* was 'supported' only by the *Canadian Journal of Anaesthesia*, to which *Anaesthesia* and the *European Journal of Anaesthesiology* had a neutral attitude. The remaining three journals had a negative effect on the *Canadian Journal of Anaesthesia*.

We examined six anaesthesia journals, three representing North America and three from Europe. A common characteristic is that they are highly rated in terms of impact factor for the specialty they represent. We chose to study these journals because of easy access, which was the same reason we included them in a previous study.[3]

The impact factor, the citation rate of a given journal for a 2-yr period, is used to quantify a journal's performance. It has been criticized extensively as it has several flaws. Differences between scientific fields, poor correlations between article citedness and journal impact, incomplete journal coverage and misprinting[1 2 4] are thought to affect negatively the value of the impact factor. None the less, the impact factor is used to rank journals in the same field. It is also used to assess a nation's publication activity in important anaesthesia journals by multiplying the impact factor by the number of articles published in a journal and the number which originated from the country(ies) assessed.[5]

High self-citing frequency may have various causes. For example, an author may prefer to submit his article on a particular topic to a journal that has previously published relevant work in that area. Therefore, more references in the author's article will be derived from articles in that particular journal. The significant correlation between self-citing rates and impact factors of the six anaesthesia journals may indicate a significant influence of self-citations on their impact factors. If the self-citing rate significantly supersedes the self-cited rate, then the journal's impact factor may be favoured by its own self-citations. But a journal's high self-citation rate may mean that a particular field of its interest is of limited scope. Low self-citation rates characterize multidisciplinary journals.[1]

In summary, a high self-citing rate may significantly affect the impact factor of a journal compared with the impact factors of other journals of the same scientific discipline. This problem could be overcome by calculating impact factors after eliminating self-citations, or correcting them by a factor for self-citations.

References

1 Science Citation Index, Journal Citation Reports. Institute for Scientific Information, Philadelphia, Pennsylvania, USA: 1997

2 Smith G. Impact factors in anaesthesia journals. *Br J Anaesth* 1996; **76**: 753–4

3 Sarantopoulos C, Fassoulaki A. Accuracy of subject and author indexes in five anaesthesia journals. *Br J Anaesth* 1995; **74**. 104–6

4 Seglen PO. Causal relationship between article citedness and journal impact. *J Am Soc Inform Sci* 1994; **45**: 1–11

5 Boldt J, Maleck W, Koetter KP. Which countries publish in important anesthesia and critical care journals? *Anesth Analg* 1999; **88**: 1175–80

British Journal of Anaesthesia 84 (2): 270P–88P (2000)

ABSTRACTS

Proceedings of the Anaesthetic Research Society Meeting

University of Edinburgh

November 11–12, 1999

*(The name of the author presenting the paper is shown in bold type. *Indicates non-member.)*
All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Can self-administered premedication reduce preoperative anxiety in day-case patients?

S. J. Clarke*, N. R. K. Anders* and A. S. Laurence
Royal Preston Hospital, Preston, UK

Day-case surgery for minor gynaecological procedures has been routine in Preston for many years, but are patients still unnecessarily apprehensive in the time leading up to surgery? We have investigated the use of self-administered premedication before arrival in hospital.

Gynaecological patients, aged 18–55 yr, ASA I–II, undergoing routine minor surgery, were recruited at the preoperative assessment clinic. Patients were given two containers, the contents of one to be taken the night before and the second before leaving home to come to hospital. All patients were accompanied to and from hospital. Patients had been allocated to one of four groups, as shown in Table 1. All three active medication groups received the same total dose of lorazepam (1 mg).

On admission, patients were presented with a linear analogue stress scale, and a second on arrival in the anaesthetic room. These scales represented no stress at one end of a 10-cm line and maximum imaginable stress at the other Routine anaesthesia was then given for the procedure. Seventeen patients were eliminated from the analysis because these stress scales had either not been given to the patient or collected. We excluded five patients who admitted to not taking the tablets and twelve others for administrative reasons (cancelled operation, etc)

All groups were significantly more stressed in the anaesthetic room compared with admission. We were surprised that the only group to show a significant reduction in anxiety was that given lorazepam 1 mg the night before, and that splitting the dose between evening and morning administration seemed to be ineffective. However, combining both groups who had some medication the night before (LP+LL) showed a significant reduction in anxiety compared with the two other groups combined (PP+PL) who only had night-time placebo, regardless of morning medication. A small premedication dose on the evening before surgery may be beneficial in some day-case patients.

Keywords: anaesthesia, day-case; premedication, lorazepam

Acknowledgement

We thank Preston and Chorley Research Fund for costs of the randomization pack.

Does self-administered premedication improve patient acceptability of day-case surgery?

N. R. K. Anders*, S. J. Clarke* and A. S. Laurence
Royal Preston Hospital, Preston, UK

Day-case surgery for minor gynaecological procedures has been routine in Preston for many years, but are patients still unnecessarily apprehensive in the time leading up to surgery? Giving patients self-administered premedication, however, may delay discharge home and patients might not actually like the tablets, or their amnesic effects at home.

Gynaecological day-case patients recruited for our previous presentation were allocated randomly to one of four premedication groups, as shown in Table 2. All were available for telephone contact and were interviewed on the first day after operation. They were asked about their well being, sleep the night before (better/same/worse), recall, pain, nausea and vomiting and whether they would have the tablets again (yes/no). We also noted the time of operation. Seventeen additional patients were excluded because of failure to contact or for administrative reasons.

Table 1 Premedication doses and anxiety scores (mean (SD) [range]) in the placebo (P) and lorazepam (L) groups. *$P<0.05$ (ANOVA), **$P<0.02$ (Student's t test)

	PP	PL	LP	LL
Evening dose	Placebo	Placebo	Lorazepam 1 mg	Lorazepam 0.5 mg
Morning dose	Placebo	Lorazepam 1 mg	Placebo	Lorazepam 0.5 mg
n	30	28	27	29
Anxiety score on admission	2.6 (1.9) [0.1–6.9]	3.2 (2.67) [0–9.8]	1.3 (1.9) [0.1–6.8]	2.2 (1.8) [0.2–5.6]
Anxiety score in anaesthetic room	4.73 (3.1) [0–10]	4.42 (1.2) [0.1–9.7]	2.24 (2.2)* [0.1–8]	3.95 (3.1) [0–10]
Combined groups	4.7 (3.1) [0–10]		3.2 (2.7) [0–10]**	

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 2 Premedication doses, time of operation, discharge time and patient follow-up for the placebo (P) and lorazepam (L) groups (mean (SD) or number). *P=0.02 (Mann–Whitney)

	PP	PL	LP	LL
Evening dose	Placebo	Placebo	Lorazepam 1 mg	Lorazepam 0.5 mg
Morning dose	Placebo	Lorazepam 1 mg	Placebo	Lorazepam 0.5 mg
n	28	26	23	29
Mean hour of op.	13.24 (2.2)	12.12 (2.3)	13.06 (2.6)	12.24 (2.8)
Discharge time (min)	150 (61)	161 (41)	162 (65)	156 (97)
Sleep preop night (B/S/W)	8/11/9	6/15/5	12/9/2	11/15/3
Combined groups	14/26/14*		23/24/5	
Have again (yes/no)	19/9	21/5	20/3	24/5

Table 3 Lung function (mean (SD)) and VAS pain scores (median) in groups 1, 2 and 3

Variable	Group	Day 0	Day 2	Day 3	Day 4
Sp_{O_2} (%)	1	97 (1.1)	93 (3.5)	94 (3.8)	94 (3.7)
	2	97 (1.6)	93 (3.0)	93 (3.6)	93 (3.1)
	3	97 (1.6)	94 (3.2)	93 (3.4)	94 (3.2)
FVC (litre)	1	2.7 (1.1)	1.3 (0.4)	1.2 (0.5)	1.3 (0.5)
	2	2.8 (0.6)	1.2 (0.6)	1.3 (0.6)	1.5 (0.6)
	3	2.8 (0.5)	1.2 (0.4)	1.3 (0.5)	1.5 (0.4)
VAS (on moving)	1	0	20	40	30
	2	0	50	35	20
	3	0.58	18	30	

Our premedication did not affect time to discharge. No patient reported problems with recall at home and there was a very low incidence of postoperative pain, and nausea and vomiting. There was no significant difference in quality of sleep on the night before operation between groups (Kruskal–Wallis). However, combining both groups who had some medication the night before (LP+LL) showed a significant improvement in sleep compared with the two other groups combined (PP+PL) who only had night-time placebo, regardless of morning medication.

There was no correlation between quality of sleep and anxiety (data from previous presentation) in any group or the whole study population (P=0.4; Spearman). Our patients had their operations throughout the morning and afternoon but interestingly, there was no correlation (P=0.5) between anxiety and time of operation. A higher dose of medication than we used is probably not appropriate for day-case patients, but a small dose of premedication the night before in day-case patients may have some benefit, rather than medication on the morning of surgery.

Keywords: anaesthesia, day-case; premedication, lorazepam

Acknowledgement

We thank Preston and Chorley Research Fund for costs of the randomization pack.

Lung function after cardiac surgery is not affected by postoperative ventilation time: an observational study

B. McGuire*, C. Royse* and A. Royse*

Departments of Anaesthesia and Cardiac Surgery, the Royal Melbourne Hospital, Victoria, Australia

Early extubation is an important part of 'fast-track' cardiac anaesthesia, but there are concerns regarding the effectiveness of spontaneous ventilation after cardiac surgery.

We identified, before operation, 100 patients undergoing elective cardiac surgery and considered suitable for early postoperative extubation. All gave informed consent for the study. Subsequent anaesthetic and postoperative management were at the discretion of the individual anaesthetist, but patients were grouped according to duration of postoperative ventilation: in group 1 (n=29), the trachea was extubated before leaving the operating room; in group 2 (n=37) within 8 h; and in group 3 (n=28) after 8 h or more. Sp_{O_2} breathing air for 5 min (using a Nellcor N200E), PEFR, FEV_1, FVC (all with a Microlab ML 3300 Spirometer) and a chest radiograph were performed before operation (day 0) and on each of the first 3 days after surgery (days 2–4). Visual analogue pain scores (0–100 mm) at rest and during movement were also recorded. Epidural analgesia was used in 23 of 29 patients in group 1 and systemic opioids in all others.

Six patients were excluded because of perioperative complications. Patient characteristics and cardiopulmonary bypass times did not differ significantly between groups, and no patient died, suffered a perioperative myocardial infarction or required re-intubation of the trachea. Lung function (Sp_{O_2}, PEFR, FEV_1 and FVC) declined significantly after surgery in each group (P<0.0001), but there was no significant difference between groups (Table 3). Radiographic changes were common in each group, but pain control was significantly better during the first postoperative day in group 1 (P<0.0001).

Lung function was significantly impaired after cardiac surgery, but this was not exaggerated by immediate extubation. However, most patients received epidural analgesia and its specific influence will be the subject of a randomized controlled study.

Keywords: surgery, cardiovascular; lung, function; ventilation, mechanical

Acknowledgements

We thank Ms J Pang and Ms K Groves for help with data collection, Mr J. Ludbrook for statistical analysis and AstraZeneca for sponsorship

Table 4 Mean (SD) respiratory variables in the two modes (controlled mechanical ventilation (CMV) and airway pressure release ventilation (APRV)) (n=8). P values (Student's t test)

	CMV	APRV	P
Pa_{CO_2} (kPa)	5.2	5.1	0.07
Ppaw (cm H_2O^{-1})	20.8 (2.5)	17.2 (2.7)	0.01
Pmaw (cm H_2O^{-1})	10.5 (0.8)	15.0 (1.8)	0.001
VE (litre min^{-1})	5.3 (1.1)	4.9 (1.1)	0.01
V_D^{aw} (ml)	81 (25)	59 (25)	0.001
V_D^{phys}/V_T	0.51 (0.04)	0.40 (0.05)	0.001
V_D^{alv}/V_T^{alv}	0.33 (0.08)	0.25 (0.08)	0.01
Phase III slope (%CO_2 litre^{-1})	4.2 (2.9)	1.6 (1.3)	0.01

Airway pressure release ventilation in cardiac surgery patients

R. P. R. Smith* and R. Fletcher

Central Manchester Hospitals NHS Trust, Manchester, UK

Airway pressure release ventilation (APRV) is more efficient than conventional controlled mechanical ventilation (CMV). Peak airway pressures and deadspace are less than with CMV.[1] APRV, with and without spontaneous breathing, has been used in acute lung injury[2] and after cardiac surgery. We have compared a modified APRV, with controlled ventilation, with CMV after cardiac surgery.

Eight patients (five males) undergoing cardiac surgery, median age 63 (range 45–74) yr, underwent ventilation with a Servo 900C ventilator after sternal closure. The inspired gas mix was air and oxygen (FI_{O_2} 0.5) with 0.5–1.0% enflurane. CMV consisted of volume controlled ventilation at 15 bpm, I:E ratio 1:2 and positive end-expiratory pressure (PEEP) of 7.5 cm H_2O. For APRV, the ventilator was set to pressure control at the same rate, I:E ratio was 2:1 and PEEP 7.5 cm H_2O. After testing for circuit leaks, patients sequentially received CMV or APRV initially. At constant end-tidal carbon dioxide concentration and carbon dioxide minute elimination ($\dot{V}_{CO_2}$), as confirmed by a Siemens 930 capnograph, we sampled arterial blood gases and recorded carbon dioxide single breath curves on a computer[3] for analysis of deadspace. The ventilator was then switched to the other mode, and new readings and blood-gas values obtained after steady state (2–5 min). Expired minute volume (VE), peak and mean airway pressures (Ppaw, Pmaw), heart rate (HR) and mean arterial pressure (MAP) were also recorded in both modes.

There were no significant differences in HR, MAP or $\dot{V}_{CO_2}$ (P>0.05) between modes. Ppaw and therefore $\dot{V}_{CO_2}/P$paw were less during APRV. Decreased airway and alveolar deadspaces, and reduced phase III slope (Table 4), suggest that prolonged inspiration of APRV allows better gas mixing, without any obvious effect on the circulation.

Keywords: lung, deadspace; lung, function; ventilation, airway pressure; ventilation, mechanical

References

1 Bratzke E, Downs JB, Smith RA. *Anesthesiology* 1988, **89**: 334–40
2 Sydow M, Burchardi H, Ephraim E, Zielmann S, Crozier TA. *Am J Respir Crit Care Med* 1994; **149**: 1550–6
3 Fletcher R, Malmqvist G, Janson L, Jonson B. *Acta Anaesthesiol Scand* 1986; **30**: 295–9

Breath interval to compare fentanyl and alfentanil i.v. in anaesthetized patients breathing spontaneously

J. A. Smart*, E. J. Pallett* and **D. J. R. Duthie**

University Department of Anaesthesia, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK

With effective regional nerve block, we have successfully used breath interval to measure the time course of dynamic effect for a single dose of fentanyl i.v.[1] This method has now been used to compare the dynamic effects of fentanyl and alfentanil.

We studied patients admitted for knee replacement surgery. Anaesthesia was induced with propofol and maintained with 0.8% isoflurane and 67% nitrous oxide in oxygen via a laryngeal mask. Sciatic and 3-in-1 femoral blocks were performed with 0.375% bupivacaine. A Capnomac Ultima (Datex) measured carbon dioxide concentrations. Its analogue output was digitized. Analysis identified a point on the downstroke of each breath. Baseline breath intervals were recorded for 5 min to exclude an effect of surgery on breath interval. Fentanyl 0.75 or alfentanil 2.25 µg kg^{-1} was then given i.v. Breath interval data were analysed using the oral absorption model of MKMODEL, extrapolating area under the curve estimates to zero.[2]

We studied 18 patients; nine received a mean dose of fentanyl 0.71 (SD 0.09) µg kg^{-1} and nine alfentanil 2.3 (0.2) µg kg^{-1}. There were four males in each group. There was no difference in mean age (fentanyl 68 (range 33–86) yr: alfentanil 61 (33–83) yr), weight (fentanyl 66 (SD 8) kg; alfentanil 77 (18) kg) or height (fentanyl 166 (8) cm; alfentanil 165 (11) cm). Time from induction of anaesthesia to administration to the opioid was 32 (14) min for the fentanyl group and 35 (15) min for the alfentanil group. Calculated opioid dynamic effects were significantly different for fentanyl and alfentanil: the rate constant of elimination was 0.0628 (0.0405) min^{-1} for fentanyl and 0.201 (0.133) min^{-1} for alfentanil (P=0.009); the elimination half-life of fentanyl was 15.2 (8.56) min and 5.04 (2.91) min for alfentanil (P=0.004). Mean residence time (MRT) for fentanyl was 23.7 (9.3) min compared with 7.0 (3.4) min for alfentanil (P<0.001) (Fig. 1)

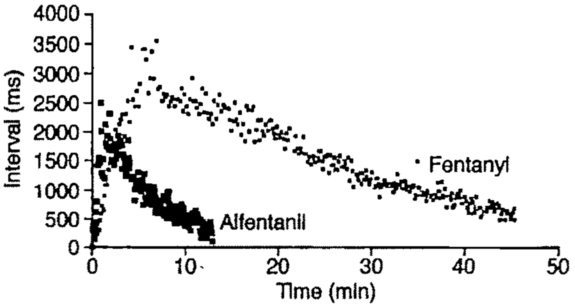


Fig 1 Breath interval (diff from baseline) after administration of alfentanil or fentanyl i.v. at time 0.

Breath interval has proved suitable to distinguish the time course of dynamic effects of fentanyl and the shorter-acting alfentanil. The dynamic MRT of fentanyl was the same as that found in ventilated patients (24 (7) min).[3] The mean dynamic elimination half-life of alfentanil was longer than 2.4 min in anaesthetized patients using respiratory inductance plethysmography.[4] These patients had no regional block and surgical stimuli may have affected the time course of the breath intervals measured.

Keywords: analgesics opioid, alfentanil; analgesics opioid, fentanyl; ventilation, spontaneous; ventilation, mechanics

References

1 Smart JA, Crone TJ, Pallett EJ, Duthie DJR. European Opioid Conference, Barcelona, April, 12 1999. *Dolor* 1999; **14** (Suppl. 1): 19
2 Holdford N. MKMODEL. Cambridge: Biosoft, 1995
3 Holmes CM. *Br J Anaesth* 1976; **48**: 907–13
4 Goodwin NW, Vanner RG, Wade JA. *Br J Anaesth* 1989; **63**: 548–53

C1-inhibitor improves the effectiveness of recombinant SP-C surfactant (r-SP-C) in a lavage-induced ARDS model

M. Leuwer[1], B. Vangerow[1]*, P G Germann[2]*, G. Marx[1]*, D. Hafner[1]* and H. Rueckoldt[1]*

[1]Department of Anesthesiology, Hannover Medical School, Hannover, Germany. [2]Department of Pathology and Toxicology and [3]Department of Respiratory Pharmacology, Byk Gulden, Konstanz, Germany

The acute respiratory distress syndrome (ARDS) is characterized by acute and diffuse injury to the endothelial and epithelial surfaces of the lung, leading to severe respiratory failure. Alterations in lung surfactant composition–function and activation of the contact system of coagulation are major contributors to the pathophysiology of ARDS. C1-inhibitor (C1-INH) is the main inhibitor of contact activation and the only known inhibitor of classical complement pathway activation. Recently, it has been shown in an animal model of ARDS that an SP-C-based surfactant containing only dipalmitoylated SP-C[1 2] was equally effective as bovine-derived surfactant preparations that contain both hydrophobic surfactant proteins SP-B and SP-C. Thus in this study we investigated the effects of administration of C1-INH and rSP-C surfactant on oxygenation and lung histology in an ARDS model.

We studied 30 male Sprague–Dawley rats subjected to repetitive lung lavage with isotonic saline solution. We used three experimental groups and two control groups: groups 1 and 2 served as controls with no treatment. Animals in group 1 were killed 60 min after the last lavage procedure. Animals in groups 3–5 received C1-INH 200 u. kg^{-1} i.v. (Centeon, Germany) (group 3), rSP-C surfactant 25 mg kg^{-1} (Byk Gulden, Germany) intratracheally (group 4) or both (group 5), 60 min after the last lavage procedure. Blood-gas values were measured 120, 150, 180 and 210 min after the last lavage procedure. All animals in groups 2–5 were killed 210 min after the last lavage procedure and the lungs were excised for histological examination. Hyaline membrane formation, distribution and the severity of intra-alveolar neutrophil (PMN) accumulation, and intra-alveolar and perivascular haemorrhage were graded semi-quantitatively using a scale from 0 to 4+. Results are presented as mean (SD). Overall variations were analysed using the Kruskal–Wallis test (non-parametric one-way analysis of variance). Subsequent comparisons between groups were made using the two-tailed Wilcoxon test and adjusted for multiple comparisons. $P<0.05$ was considered statistically significant,

At 210 min after the last lavage procedure, P_{O_2} values in group 4 (456±74 mm Hg) and group 5 (387±155 mm Hg) were significantly higher than those in group 3 (120±103 mm Hg) and in controls (63±12 mm Hg). The grading for PMN infiltration was significantly lower in animals who received Cl-INH (group 3=2.0,.group 5=2.3) than in controls (group 2=2.7) or in those treated with r-SP-C surfactant only (group 4=3.3), The severity of intra-alveolar haemorrhage and oedema were significantly reduced in group 3 and highest in group 4.

In this lavage-induced ARDS model, Cl-INH increased the effectiveness of r-SP-C surfactant application by reducing the inflammatory response to surfactant treatment.

Keywords: lung, adult respiratory distress syndrome; lung, surfactant; lung, model; rat

References

1 Hafner D, Beume R, Kilian U, Krasznai G, Lachmann B. *Br J Pharmacol* 1995; **115**: 451–8
2 Hafner D, Germann PG, Hauschke D. *Br J Pharmacol* 1998, **124**. 1083–90

Effect of arterial–mixed venous oxygen content difference on indices of pulmonary oxygen transfer in an ARDS lung model

M. Nirmalan, T. Willard, M. O. Columb and P. Nightingale

University Department of Anaesthesia and MRC Trauma Group, North Western Medical Physics and Intensive Care Unit, South Manchester University Hospitals, Manchester, UK

Several oxygen tension and content based indices are used to quantify pulmonary oxygen transfer. Although tension based indices are inherently $F\text{I}_{\text{O}_2}$-dependent, they are used widely in clinical practice, including in the diagnosis and stratification of ARDS patients. The assumption that arterial–mixed venous oxygen content difference ($C\text{a}_{\text{O}_2}$–$C\text{v}_{\text{O}_2}$) remains constant is common to any analysis of impaired pulmonary oxygen transfer using measurements from arterial blood and inspired gas. $C\text{a}_{\text{O}_2}$–$C\text{v}_{\text{O}_2}$ is, however, subject to considerable variability in critical illness[1] and the impact of this variability on indices of pulmonary oxygen transfer has not been evaluated in a clinical setting In this study, we estimated the effect of $C\text{a}_{\text{O}_2}$–$C\text{v}_{\text{O}_2}$ on venous admixture ($Q\text{s}/Q\text{t}$), calculated content difference between end-capillary and arterial blood ($C\text{c}'_{\text{O}_2}$–$C\text{a}_{\text{O}_2}$), $P\text{a}_{\text{O}_2}/F\text{I}_{\text{O}_2}$ ratio and alveolar–arterial oxygen tension gradient ($P\text{A}_{\text{O}_2}$–$P\text{a}_{\text{O}_2}$) in an ARDS lung model.

A multicompartment lung model described by West[2] was modified by incorporating $V\text{A}/Q$ scatter data from 16 ARDS patients obtained using an inert gas elimination technique.[3] To validate the model, 55 arterial and mixed venous blood-gas measurements were obtained from 10 ARDS patients (4–7 measurements per patient). Predicted and measured $P\text{a}_{\text{O}_2}$ values were compared using analysis of covariance (ANCOVA) to determine the within-subject correlation coefficient (r). Agreement was assessed using intra-class correlation coefficient (r_i) and Bland–Altman plots. The model lung was used in the subsequent appraisal of four commonly used indices of pulmonary oxygen transfer. Shunt and deadspace in the model lung were 40.7% and 28.8%, respectively. Approximately 7% of cardiac output perfused alveolar units with $V\text{A}/Q$ values of 0.01–0.005, and 10% perfused units with a $V\text{A}/Q$ <0.1.

Validation showed lognormal distributions for both predicted and measured $P\text{a}_{\text{O}_2}$ values. ANCOVA showed r=0.93 (r^2=0.87, $P<0.001$). Agreement assessed by r_i was 0.91. All four indices showed changes with $F\text{I}_{\text{O}_2}$ and $C\text{a}_{\text{O}_2}$–$C\text{v}_{\text{O}_2}$. However, the magnitude of changes in $V\text{A}/Q$ caused by variations in $C\text{a}_{\text{O}_2}$–$C\text{v}_{\text{O}_2}$ or $F\text{I}_{\text{O}_2}$ was small (<2%) and hence clinically unimportant. Variations in the other three indices were considerably greater and likely to be clinically misleading $P\text{a}_{\text{O}_2}/F\text{I}_{\text{O}_2}$ ratio was found to be an unsatisfactory measure of pulmonary oxygen transfer even in the higher $F\text{I}_{\text{O}_2}$ range. This study shows there is no substitute for measured shunt fraction when accurate estimation of pulmonary oxygen transfer is required.

Keywords: lung, adult respiratory distress syndrome; lung, model; lung, shunting; oxygen, partial pressure

Table 5 Serum concentrations of S100β protein 6 h after surgery correlated with age, postoperative jugular bulb saturation (Sj_{O_2}), cerebral arterial venous difference in lactate during rewarming (AVDL 36°C) and lactated Ringer's in the cardiopulmonary bypass (CPB) prime

Variable	β	95% CI for β		*t*	*P*
Age	0.029	0.016	0.043	4.387	<0.001
Postoperative Sj_{O_2}	0.024	0.007	0.040	2.865	0.005
Lactated prime=0	0.481	0.087	0.875	2.426	0.017
AVDL at 36°C on CPB	–1.9	–3.793	–0.006	–1.993	0.049
Arterial lactate 10 min CPB	0.084	–0.325	0.493	0.407	0.685

References

1 Nirmalan M, Willard T, Khan A, Nightingale P. *Br J Anaesth* 1998; **80**: 829–31

2 West JB. *Ventilation/Blood Flow and Gas Exchange*, 3rd Edn. Oxford: Blackwell Scientific Publications, 1980; 33–52

3 Dantzker DR, Brook CJ, Dehart P, Lynch JP, Weg JD. *Am Rev Respir Dis* 1979; **120**: 1039–52

Perioperative factors affecting serum S100β concentration after coronary artery surgery

M. J. A. Robson*, R. P Alston, P J. D Andrews and M. J. Souter

Department of Anaesthetics, Royal Infirmary of Edinburgh, Edinburgh EH3 9YW, UK

S100β protein continues to be assessed as a marker of cerebral damage after coronary artery surgery (CAS).[1] Its release correlates positively with age, and greater postoperative concentrations are found with stroke and encephalopathy.[2] However, the mechanism of its release is unclear. As part of a larger study, we report serum concentrations of S100β protein, 6 h after CAS, in relation to age, postoperative jugular bulb saturation (Sj_{O_2}), cerebral arterial venous difference in lactate during rewarming (AVDL 36°C) and lactated Ringer's in the cardiopulmonary bypass (CPB) prime.

We studied 86 men and 11 women, mean age 60 (SD=9) yr. Lactated Ringer's solution was used to prime the CPB circuit in 51 patients and a non-lactated prime in 46. A catheter was positioned in the right jugular bulb. Paired jugular bulb and arterial samples were obtained for Sj_{O_2} and lactate concentrations before CPB, 10 min during CPB, before re-warming, at 36°C, on arrival in the ICU, and 1, 2 and 6 h thereafter. A serum sample obtained at 6 h was stored at –20°C for S100β assay. The influence of predictive variables on S100β was assessed by general linear modelling univariate analysis. Results are presented in Table 5.

Lower concentrations of S100β protein were associated with the use of lactated prime solution. However, the arterial lactate concentration achieved after 10 min of CPB was not a significant factor. The negative relationship with AVDL during rewarming suggests that failure of lactate use and cerebral lactate production may be associated with S100β production. The positive correlation with postoperative Sj_{O_2} may represent increased washout or a possible causative mechanism through facilitated production of oxygen-free radicals.[3] Further research is required to determine the specific role of these factors on S100β release and their relationship with cerebral damage after CAS

Keywords: protein, S100β; surgery, cardiovascular

Acknowledgement

Funded by Wellcome Trust grant No 050190.

References

1 Taggart DP, Mazel JW, Bhattacharya K, *et al. Ann Thorac Surg* 1997; **63**: 492–6

2 Jonsson H, Johnsson P, Alling C, Westady S, Blomquist S. *Ann Thorac Surg* 1998; **81**: 266–7

3 Khaliq-AH, Blasig IE, Baur MO, Hohlfeld M, Meskhishvili-AV, Lange PE. *J Thorac Cardiovasc Surg* 1999, **117**. 1027–8

Cerebral oxygenation during normocapnic hyperoxia: comparison of tissue microprobes, spatially resolved near infrared spectroscopy and jugular venous oximetry

A. D. M. McLeod*, M Smith, F. Igielman* and J. C Goldstone*

Department of Neuroanaesthesia, National Hospital for Neurology and Neurosurgery, UCL Hospitals, London WC1N 3BG, UK

Jugular venous oximetry (Sj_{O_2}) is used to assess the adequacy of cerebral oxygenation but reflects only global changes, whereas brain tissue microprobes can directly record tissue oxygen tension[1] (Pbr_{O_2}) within a region close to the probe tip. Alternatively, near infrared spectroscopy (NIRS) allows non-invasive measurement of changes in cerebral oxygenation and, more recently, direct assessment of cerebral oxygen saturation (Sc_{O_2}).[2] In this study, we have compared changes in cerebral oxygenation assessed by simultaneous measurement of Sj_{O_2}, Pbr_{O_2} and Sc_{O_2} during normocapnic hyperoxygenation in brain-injured patients

Five severely head-injured patients requiring invasive monitoring in the neurosurgical ICU were studied. Monitoring included intracranial pressure and Sj_{O_2} (Opticath, Abbot). A Neurotrend (Codman) multi-parameter sensor (tissue P_{O_2}, P_{CO_2} and pH) was inserted into the frontal cortex distant from any area of contusion. Sc_{O_2} was measured using spatially resolved spectroscopy (NIRO 300, Hamamatsu Photonics, Japan) with optodes (40 mm separation) placed over the frontal region close to the tissue probe. Normal management procedures were continued during the study. Sj_{O_2}, Pbr_{O_2} and Sc_{O_2} data were recorded onto a PC at 1-s intervals. Patients' lungs were ventilated at their pre-existing FI_{O_2} for a 10-min baseline period before an increase in FI_{O_2} to 100% for 30 min. FI_{O_2} was then decreased to 60% for another 30 min and finally to 2–5% below baseline for 20 min before returning to the starting FI_{O_2}. Pa_{O_2} was measured after equilibration at each FI_{O_2}. For the cerebral oxygenation variables, a mean value for the final 10 min of each equilibration period was used as a summary measure. Results for all patients are shown in Table 6. Data were analysed using analysis of variance and a paired *t* test, where indicated.

This study is the first to compare simultaneous measurements of Sj_{O_2}, Pbr_{O_2} and Sc_{O_2} during normocapnic hyperoxia. The relative magnitude of changes in Sj_{O_2}, Pbr_{O_2} and Sc_{O_2} for a given change in Pa_{O_2} varied widely between patients, but the direction of change was the same. Direct comparisons between different physiological variables is difficult, as the relationships may not be linear. NIRS is a useful tool for non-invasive measurement of cerebral oxygenation but its relation to other monitoring techniques requires further investigation.

Keywords: brain, oxygen consumption; oxygen, saturation;

Table 6 Mean (SD) changes in cerebral oxygenation assessed by measurement of jugular venous oximetry Sj_{O_2}, tissue oxygen tension in the brain Pbr_{O_2} and cerebral oxygen saturation Sc_{O_2} at different FI_{O_2} values in brain-injured patients *Significant difference from baseline ($P<0.05$ with Bonferroni correction)

	Baseline	FI_{O_2} 100%	FI_{O_2} 60%	FI_{O_2} 2–5% below baseline
Pa_{O_2} (kPa)	14.74 (1.52)	62.66 (6.59)*	31.31 (5.86)*	11.46 (0.71)*
Sc_{O_2} (%)	78.02 (4.10)	83.19 (5.85)	80.51 (4.75)	76.53 (3.6)
Pbr_{O_2} (kPa)	4.08 (0.82)	20.17 (7.40)*	8.44 (2.52)*	4.08 (0.57)
Sj_{O_2} (%)	80.17 (7.54)	90.19 (6.38)	84.40 (9.27)	78.97 (8.25)

Table 7 Volume measurements (cm^3) of the brain and ventricular system in each woman

		Gestation (weeks)		
	Pre-pregnant	25	37/39	6 weeks post partum
Subject No. 1				
Brain	1197.4	1187.3	1150.7	1180.1
Ventricles	6.7	7.1	9.5	6.8
Subject No. 2				
Brain	1304.3	1240.4	1208.7	1264.2
Ventricles	17.2	19.9	21.3	18.0

oxygen, partial pressure; measurement techniques, near infrared spectroscopy

References

1 van Santbrink H, Maas AIR, Avezaat CJJ *Neurosurgery* 1996; **38**: 21–31
2 Owen-Reece H, Smith M, Elwell CE, Goldstone JC. *Br J Anaesth* 1999; **82**: 418–26

Quantification of brain size during parturition

A. Holdcroft, A. Oatridge*, G. Jenkinson*, A. Herlihy*, A. Hall*, L. Fusi* and G. M. Bydder*

Imperial College School of Medicine, Hammersmith Hospital, London W12 0HS, UK

We have demonstrated a qualitative increase in maternal brain size in the last month of pregnancy and 6 weeks after delivery using accurately registered and subtracted magnetic resonance images.[1] This is a further longitudinal study of normal females before, during and after pregnancy.

Subvoxel registration of serial three-dimensional T1-weighted images acquired on a 1.0 T Picker HPQ system was used to detect changes to the brain and surrounding cerebrospinal fluid. In each case the initial pre-pregnant scan was used as the baseline image to which all subsequent images were matched. A quantification procedure designed to calculate the brain and ventricular sizes separately was applied to the registered anatomical images. Contours were drawn around the brain and lateral ventricles separately to define the regions of interest and an automated quantification programme which included a contour detection algorithm and a thresholding technique, was used to calculate volume.[2]

The first woman had a control scan before pregnancy, then every 5 weeks from 15 weeks until 35 weeks, at 37 weeks' gestation and at 6, 24, 40 and 52 weeks after delivery. The second woman was studied at the same intervals during pregnancy at 25 and 39 weeks' gestation and from 6 weeks post partum. The volume measurements for the brain and ventricular system are shown in Table 7. An increase in ventricular volume was measured starting as early as 15 weeks' gestation and was associated with a corresponding decrease in brain size. In the first woman, a 40% increase in ventricular size was measured and a 4% reduction in brain size from her non-pregnant value. After delivery, the brain gradually increased in size and reached a maximum at approximately 24 weeks post partum when it appeared to return to its original size. The second woman showed changes of 24% and 7%, respectively.

Keywords: pregnancy; brain, magnetic resonance imaging

Acknowledgement

Funded in part by the MRC and Obstetric Anaesthetists' Association

References

1 Holdcroft A, Oatridge A, Hajnal JV, Bydder GM *J Physiol* 1997; **499**: 79–80P
2 Saeed N, Puri BK, Oatridge A. *Magn Reson Imaging* 1998; **16**: 1237–47

Jugular bulb oxyhaemoglobin saturation after cardiac surgery: effect of weaning from mechanical ventilation

S. S. Liau*, R P Alston and M. J. A. Robson*

Departments of Anaesthetics and Cardiothoracic Surgery, Royal Infirmary of Edinburgh, Edinburgh, UK

We have observed an increase in jugular bulb oxyhaemoglobin saturation (Sjv_{O_2}) during weaning from intermittent positive pressure ventilation after cardiac surgery. The timing of weaning therefore may influence the duration of Sjv_{O_2} desaturation (Sjv_{O_2} <50%).[1] In this study, we determined if Sjv_{O_2} increases with onset of spontaneous ventilation and examined the influence of cardiorespiratory function on any change. The influence of time to spontaneous ventilation and tracheal extubation on duration of Sjv_{O_2} <50% was also studied.

We retrospectively reviewed 126 patients undergoing coronary artery bypass grafting. Initiation of spontaneous ventilation was defined as the time when ventilatory frequency (*f*), measured by capnography, changed from a constant rate to one that fluctuated for a sustained period. This was identified clearly in 34 patients. After induction of anaesthesia, a fibreoptic oximetry catheter was inserted to lie in the right jugular bulb. Arterial oxyhaemoglobin saturation (Sp_{O_2}), mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), end-tidal carbon dioxide concentration (PE'_{CO_2}) and f were recorded every minute. Mean values of each variable, including cerebral perfusion pressure (CPP), were calculated over a 30-min period before and after the onset of spontaneous ventilation.

Paired Student's t test found that the increase in Sjv_{O_2}, MAP, HR, CPP, f and the decrease in CVP with the onset of spontaneous ventilation were significant ($P<0.05$). Changes in PE'_{CO_2} and Sp_{O_2} were not significant. Stepwise multiple regression showed that the change in Sjv_{O_2} was directly dependent on the change in PE'_{CO_2} ($B=2.979$, $P=0.04$). Using Pearson's correlation, there was no significant relationship between the total duration of Sjv_{O_2} <50% and either time to spontaneous ventilation or tracheal extubation in the group as a whole. In the 15 patients who experienced episodes of desaturation, there was a positive relationship between total duration of Sjv_{O_2} <50% and time to spontaneous ventilation ($r=0.564$, $P=0.029$), but not tracheal extubation.

If the change in f from a constant to irregular pattern truly represents the onset of spontaneous ventilation, the results of this study suggest that it is associated with an increase in Sjv_{O_2} and that it is partly accounted for by change in PE'_{CO_2}. Furthermore, in patients with episodes of desaturation, total duration of Sjv_{O_2} <50% is influenced by the time to spontaneous ventilation. However, these findings require confirmation in prospective studies.

Keywords: measurement techniques, oximetry; ventilation, mechanical; surgery, cardiovascular; oxygen, saturation

Acknowledgement

Funded by The Wellcome Trust No. 050190.

Reference

1 Souter MJ, Andrews PJD, Alston RP. *Br J Anaesth* 1998; **81**: 239–41

Effect of epidural epinephrine on the minimum local analgesic concentration (MLAC) of epidural bupivacaine in labour

L. S. Polley*, **M. O. Columb**, N. N. Naughton* and D. S. Wagner*

University of Michigan Medical Center, Ann Arbor, MI 48109, USA

Whether the addition of epinephrine to local anaesthetic solutions used for epidural labour analgesia is subject to debate. Previous reports on analgesic and haemodynamic effects have been conflicting. The minimum local analgesic concentration (MLAC)[1] has been defined as the median effective local analgesic concentration (EC_{50}) in the first stage of labour. Our aim was to determine the local anaesthetic sparing efficacy of epidural epinephrine by its effect on the MLAC of bupivacaine.

We studied women requesting epidural analgesia at ≤7 cm cervical dilatation and who had not received opioids. Patients were allocated randomly to one of two groups in this double-blind, up–down sequential allocation study. After placing a lumbar epidural catheter, 20 ml of the test solution was given; bupivacaine ($n=35$) or bupivacaine with epinephrine 1:300 000 ($n=33$). The test dose was omitted for the purposes of the study. The concentration was determined by the response of the previous patient to a higher or lower concentration. Analgesic efficacy was assessed using 100-mm visual analogue pain scores (VAPS). Efficacy was defined as a VAPS of 10 mm or less during contractions within 30 min. MLAC was determined using the up–down method of independent pairs and by probit regression as a back-up sensitivity test.

Table 8 Estimates of the minimum local analgesic concentration (MLAC) or EC_{50} (95% confidence interval) in the two groups determined using the up–down (UD) method of independent pairs and by probit regression. *Student's t test $P=0.024$, 95% CI difference 0.003, 0.035 %w/v

Group	MLAC (%w/v) (UD method)*	EC_{50} (%w/v) (probit)
Bupivacaine	0.091 (0.081, 0.102)	0.099 (0.086, 0.113)
Bupivacaine+epinephrine	0.070 (0.054, 0.086)	0.066 (0.048, 0.089)

Patient data, obstetric characteristics and maternal haemodynamics were similar in the two groups. There were significant reductions in fetal heart rate ($P=0.0034$) and variability in the bupivacaine–epinephrine group ($P<0.0001$). MLAC results are shown in Table 8.

Addition of epinephrine resulted in a statistically significant reduction (23%, $P=0.024$) in the MLAC of bupivacaine. However, the clinical significance of this may be questioned as greater reductions have been described for fentanyl (72%)[2] and sufentanil (91%).[3] A dose-dependent reduction in MLAC may have occurred with higher doses of epinephrine but the reduction in fetal heart rate variability must limit this. In conclusion, while epinephrine can be shown to significantly reduce the MLAC of bupivacaine in a statistical sense, clinical significance does not necessarily follow.

Keywords. analgesia, obstetric, analgesic techniques, epidural; anaesthetics local, bupivacaine; sympathetic nervous system, epinephrine

References

1 Columb MO, Lyons G. *Anesth Analg* 1995; **81**: 833–7

2 Lyons G, Columb MO, Hawethorne L, Dresner M. *Br J Anaesth* 1997; **78**: 439–7

3 Polley LS, Columb MO, Wagner DS, Naughton NN. *Anesthesiology* 1998; **89**: 626–32

Effect of intrathecal fentanyl on the minimum local analgesic dose of intrathecal bupivacaine in labour

G. M. Stocks*, R Fernando*, S. P Hallworth*, A. J. England, M. O Columb and G. Lyons

Departments of Anaesthesia, Royal Free Hospital, London, South Manchester University Hospital, Withington and St James' University Hospital, Leeds, UK

Although various combinations of local anaesthetics and opioids are used intrathecally for combined–spinal epidural (CSE) analgesia in labour, there is little published on the analgesic dose–response relationships of these drugs. A clinical model has been described to estimate the minimum local analgesic concentration (MLAC) of epidural local anaesthetics for analgesia in labour.[1] Our aim was to apply the same clinical model to estimate the minimum local analgesic dose (MLAD) of intrathecal bupivacaine in the first stage of labour and define this as the median effective dose (ED_{50}). In addition, we wished to estimate the local anaesthetic sparing effect when combined with fentanyl 25 µg intrathecally.

We studied 60 women at 2–6 cm cervical dilatation, requesting regional analgesia for labour pain, allocated randomly to receive either bupivacaine alone or bupivacaine with fentanyl 25 µg as the intrathecal component of CSE analgesia, according to a double-

Table 9 Minimum local analgesic dose (MLAD) of intrathecal bupivacaine in the two groups (95% confidence intervals) *MLAD difference $P<0.0001$, 95% CI difference 0.72, 1.56

Group ($n=30$)	MLAD ED_{50} (mg)*	Probit ED_{50} (mg)
Bupivacaine	1.99 (1.71, 2.27)	1.75 (1.46, 2.09)
Bupivacaine+fentanyl 25 μg	0.85 (0.58, 1.13)	0.76 (0.55, 1.05)

blind sequential allocation procedure. The CSE procedure was performed with patients in the sitting position and intrathecal placement of the spinal needle was confirmed by aspirating cerebrospinal fluid before and after injection of drug. The first patient studied in each group received bupivacaine 2.25 mg. Subsequent patients received doses that were determined by the analgesic response of the previous patient in that group according to up–down sequential allocation. Analgesia was assessed using a 100-mm visual analogue pain score (VAPS) at 5-min intervals for 15 min after intrathecal injection. An effective dose, defined as a VAPS of 10 mm or less within 15 min of injection, directed a decrement of 0.25 mg of bupivacaine for the next patient within that group. An ineffective dose, defined as a VAPS of greater than 10 mm after 15 min of injection, directed an increase of 0.25 mg of bupivacaine for the next patient in that group. MLAD was estimated using the method of Dixon and Massey[2] and by probit regression analysis as a back-up sensitivity test, with $P<0.05$ taken as statistically significant.

Obstetric and patient characteristics were similar in the two groups except for a significantly higher incidence of primiparous women in the bupivacaine only group (77% *vs* 47%, $P=0.033$). The MLAD results are shown in Table 9. Twenty-two patients in Bup+fent group and zero in Bup alone experienced pruritus.

The MLAD of intrathecal bupivacaine in early labour was 1.99 mg. Fentanyl 25 μg resulted in significant bupivacaine dose sparing by a factor of 2.3 (95% CI 1.7, 3.4) for the parturients in this study.

Keywords: analgesia, obstetric; anaesthetics local, bupivacaine, analgesics opioid, fentanyl

Acknowledgement

Dr Stocks is a research fellow funded by the Obstetric Anaesthetists' Association

References

1 Columb MO, Lyons G. *Anesth Analg* 1995, **81**. 833–7
2 *Introduction to Statistical Analysis* New York: McGraw Hill, 1983; 428–39

Thrombelastography identifies gender related differences in clotting

H. Gorton*, E. Warren*, G. Lyons and M Columb

St James's University Hospital, Leeds LS9 7TF, UK

Thrombelastography (TEG) is influenced by normal pregnancy, with changes indicating hypercoagulability compared with non-pregnant controls.[1] We sought to determine TEG differences between male and non-pregnant female volunteers.

We performed TEG in 150 volunteers: male ($n=50$), female ($n=50$) and pregnant women ($n=50$). All volunteers were ASA I or II. TEG samples were obtained in an established, standardized manner. TEG variables (r (mm), k (mm), α angle (°), maximum amplitude (mm)) and patient characteristics were recorded. Kruskal–Wallis analysis was used to test for significant ($P<0.05$) differences between groups and Dunn's post-test was used for multiple comparisons.

For r and k values, α angle and maximum amplitude, differences between the three groups were significant for all comparisons ($P<0.01$ to <0.001). There was a trend ($P<0.0001$) suggesting increasing coagulability from the male, through to the female, to the pregnant female group (Fig. 2).

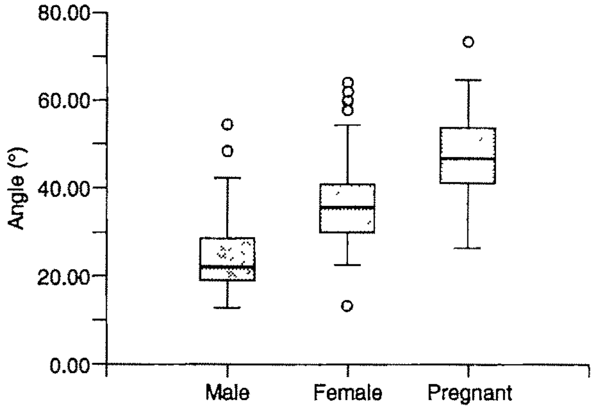


Fig 2 Changes in alpha angle from the male, through to the female, to the pregnant female group Outliers, 2.5, 25, 50, 75 and 97.5 centiles are shown.

We have demonstrated a significant difference in four TEG variables between male and non-pregnant female volunteers This difference may be attributable to sex hormones.

Keywords: blood, coagulation; measurement techniques, thombelastography

Reference

1 Sharma SK. *Anesth Analg* 1997; **85**. 94–8

Prevention of spinal anaesthesia-induced hypotension during Caesarean section: comparative study of pre-emptive vasopressors

B Ayorinde, **J. Brown***, P. Buczkowski*, J. Shah and D J Buggy

University Department of Anaesthesia, Leicester General Hospital, Leicester, UK

The incidence of hypotension after spinal anaesthesia for Caesarean section is almost 80%, despite lateral uterine displacement, fluid preload and vasopressors. Recent work indicates that i.v. vasopressors are preferable to fluid preload, with ephedrine being the vasopressor of choice,[1] but phenylephrine i.v has also been shown to be safe and effective.[2] A preliminary report suggested that ephedrine i.m provides better cardiovascular support than ephedrine i.v.[3] Our objective was to evaluate prophylactic phenylephrine i.m. compared with ephedrine i.m., in terms of haemodynamic stability and further vasopressor requirements, in patients undergoing spinal anaesthesia for Caesarean section, in a double-blind, placebo-controlled study.

We studied 108 ASA I women undergoing elective Caesarean section, allocated randomly by a sealed envelope technique to one of four groups, each receiving an identical, coded i.m. injection immediately after intrathecal administration of 0.5% hyperbaric bupivacaine 2.2 ml and fentanyl 20 μg. Group 1 received phenylephrine 4 mg i.m., group 2 phenylephrine 2 mg i.m., group 3 ephedrine 45 mg i.m. and group 4 saline i.m. All patients

Table 10 Total rescue ephedrine dose required and percentage reduction in MAP in the four groups (mean (SD)) $*P<0.05$, ephedrine 45 mg *vs* saline, $**P<0.02$, phenylephrine 4 mg *vs* saline

	Phenylephrine 4 mg	Phenylephrine 2 mg	Ephedrine 45 mg	Saline
Total ephedrine (mg)	15.9 (15.8)**	17.9 (15.0)	16.4 (15.5)*	28.8 (21.0)
% Change in MAP	–21.3 (14.9)**	–35.0 (16.2)	–22.4 (14.1)*	–32.0 (17.1)

received a standard combined spinal–epidural technique in the sitting position. Mean arterial pressure (MAP) and heart rate (HR) were recorded using an automated, non-invasive monitor at 1-min intervals. Hypotension was defined as a 25% decrease in MAP from baseline, which was taken as the lowest MAP value recorded before receiving the study medication. Rescue i.v. bolus doses of ephedrine were given if patients reported nausea, dizziness or were hypotensive.

All groups were similar in age, weight, parity, median dermatomal sensory level and baseline haemodynamic data There was a rapid decrease in MAP ($P<0.01$) and a high incidence of hypotension in all groups (39–72%). Patients receiving phenylephrine 4 mg i.m. and ephedrine 45 mg i.m. had significantly less percentage reduction in MAP and although there was no difference in time to first requirement for rescue i.v. ephedrine, total rescue ephedrine dose required in these two groups was less compared with controls and phenylephrine 2 mg i.m. (Table 10). Umbilical cord venous blood pH and Apgar scores were similar in all groups.

We conclude that phenylephrine 4 mg i.m. and ephedrine 45 mg i.m., given pre-emptively at induction of spinal anaesthesia, reduced the severity of hypotension and total dose of rescue i.v. ephedrine, but not the incidence of hypotension, after spinal anaesthesia for Caesarean section.

Keywords: anaesthesia, obstetric; anaesthetic techniques, spinal; complications, hypotension; sympathetic nervous system, phenylephrine; sympathetic nervous system, ephedrine

References

1 Jackson R, Reid J, Thorburn J. *Br J Anaesth* 1995; **75**: 262–5
2 Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ. *Br J Anaesth* 1996; **76**: 61–5
3 Webb A, Shipton EA. *Can J Anaesth* 1998; **45**: 367–9

Comparison of the static rate of regulation with the transient hyperaemic response test to assess changes in cerebral autoregulation

R. K. Tibble*, K J Girling and R. P. Mahajan

University Department of Anaesthesia, Queen's Medical Centre and City Hospital, Nottingham, UK

Transcranial Doppler ultrasonography is used to assess cerebral autoregulation by measuring the middle cerebral artery flow velocity (*v*mca) before and after a stepwise change in mean arterial pressure (MAP), allowing calculation of the static rate of regulation (sROR).[1] The transient hyperaemic response (THR) test has also been used to assess cerebral autoregulation, using the transient hyperaemic response ratio (THRR) and the strength of autoregulation (SA) as indices.[2] We assessed if changes in sROR, during administration of incremental concentrations of desflurane, were reflected by changes in THRR and SA.

In seven patients (ASA I or II), aged 18–50 yr, baseline MAP, end-tidal carbon dioxide (E'_{CO_2}) partial pressure and *v*mca were recorded after sedation with propofol infusion to a target blood concentration of 1 µg ml^{-1}. Two THR tests were performed using ipsilateral common carotid artery compression for 10 s. To calculate sROR, *v*mca recordings were repeated after an increase in MAP (of at least 15%) induced by phenylephrine Anaesthesia was then induced with propofol and the tests were repeated after equilibration (15 min) at 0.5 MAC of desflurane and then at 1.5 MAC of desflurane in 50% nitrous oxide and oxygen. The propofol infusion was continued throughout at a target blood concentration of 1 µg ml^{-1}. Baseline MAP and E'_{CO_2} partial pressure were maintained by infusion of phenylephrine and adjustments in ventilation, respectively. THRR, SA and sROR were calculated using established methods.[1 2] Repeated measure ANOVA tests were applied for changes in autoregulatory indices.

Table 11 shows mean values for sROR, SA and THRR for seven subjects. Incremental concentrations of desflurane caused significant impairment of cerebral autoregulation ($P\leq0.001$) at each stage, as assessed by all three indices.

Changes in cerebral autoregulation during incremental administration of desflurane, as assessed by sROR, are reflected by the indices derived from the THR test.

Keywords: brain, blood flow; measurement techniques, blood flow, brain

References

1 Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. *Anesthesiology* 1995; **83**. 66–76
2 Mahajan RP, Cavill G, Simpson EJ. *Anesth Analg* 1998; **87**: 843–9

Blink duration: a function of anaesthetic sedation

A. K. Jandziol*, M. Prabhu[1]*, R. H. S. Carpenter[2]* and J G. Jones[1]

[1]*University Department of Anaesthesia, Addenbrooke's Hospital, Cambridge, UK.* [2]*Physiological Laboratory, Downing St, University of Cambridge, Cambridge, UK*

Our aim was to establish if eye blink duration was useful in

Table 11 Mean (SD) values for the static rate of regulation (sROR), strength of autoregulation (SA) and the transient hyperaemic response ratio (THRR) for seven subjects before and after induction of anaesthesia with desflurane MAP=Mean arterial pressure

	THRR	SA	sROR	MAP increase (%)
Pre-induction	1.43 (0.19)	1.10 (0.13)	67.73 (9.43)	22.47 (6.34)
0.5 MAC	1.21 (0.10)	0.86 (0.08)	52.47 (21.1)	23.01 (2.05)
1.5 MAC	1.09 (0.05)	0.77 (0.07)	30.74 (18.4)	23.68 (5.66)

quantifying the sedative effects of 0.05 and 0.1 minimum alveolar concentration (MAC) of sevoflurane.

An infrared emitter and detector mounted on a headset was used to measure the duration of eye blink in eight healthy volunteers. The signals were analysed using the Cambridge Research Systems Epic Compact 6 software package. Baseline measurements of blink duration were performed with subjects wearing a noseclip and breathing 100% oxygen through a mouthpiece. This was followed by low doses of sevoflurane administered over 15-min periods to achieve 0.05 and 0.1 MAC. End-tidal sevoflurane was measured using a Datex Capnomac Ultima monitor. MAC values were adjusted for age for each subject using the formula: $\text{MAC}=a\times10^{bx}$ (where x=age−40, b=−0.00269 and a=1.81 for sevoflurane)[1] Towards the end of each 15-min period, blink duration was measured for 2 min. There followed a 15-min period of sevoflurane 'washout' during which time blink duration was measured at 3-min intervals Subjects were unaware of the commencement, concentration or discontinuation of administered sevoflurane. A 10-cm visual analogue scale (VAS) was used at intervals throughout the study. The scale was marked 'fully alert' to 'can't keep eyes open'. Statistical analysis was performed using the Mann–Whitney U test ($P<0.05$ was considered statistically significant). Blink duration was expressed in median (interquartile range (IQR)) ms.

During the baseline measurement period blinks were all shorter than 760 ms in all subjects (median duration = 98 ms, IQR = 30 ms). With end-tidal sevoflurane at 0.05 MAC, all subjects demonstrated a statistically significant prolongation in eye blink duration (median = 198 ms, IQR = 83 ms, $P<0.0117$) With end-tidal sevoflurane at 0.1 MAC, blink duration was prolonged compared to baseline (median = 210 ms, IQR = 850 ms, $P<0.0117$), but when comparing 0.05 and 0.1 MAC, there was no significant difference ($P<0.4$) After discontinuation of 0.1 MAC of sevoflurane the recovery half-life of the median blink duration was 13.4 min. The VAS scores at baseline, 0.05 and 0.1 MAC were respectively 2.7±2.41 (SD) 6.2±2.8 and 6.1±3.3.

The results suggest that eye blink duration may be a method of measuring sedative effects of very low doses of sevoflurane These results also indicate the half time recovery of the median blink duration is 13.4 min after discontinuation of 0.1 MAC of sevoflurane. Further work needs to be done to determine if eye blink duration can be used to determine 'street fitness' after anaesthesia.

Keywords: sedation; eye, blink; anaesthesia, depth

Reference

1 Mapleson WW. *Br J Anaesth* 1996; **76**: 179–85

Assessing the filtration performance of breathing system filters using salt particles

A. R. Wilkes

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, UK

Challenging with salt particles is a standard method of determining the filtration efficiency of respiratory protective devices.[1] The efficiency of filters varies with the size of the aerosol droplets or particles in the challenge and, from theory, there is a size of particle which most readily passes through filters. These most penetrating particles are typically 0.1–0.3 μm in diameter. The standard for respiratory protective devices specifies using salt particles with a mass mean diameter of 0.26 μm[1] to obtain the 'worst-case' level of efficiency.

The filtration efficiency of 12 breathing system filters (BSF) was measured previously using bacterial and viral challenges[2] The filtration performance of five samples of each of these BSF (five pleated hydrophobic and seven electrostatic filters) was measured using the test method specified for respiratory protective devices.[1] Salt (sodium chloride) particles with a mass median aerodynamic diameter of 0.26 μm were generated and penetration (ratio of the number of particles passing through the BSF to the number of particles in the challenge) measured using laser photometers (AFT 8130, TSI Inc., St. Paul, USA). Flow through the filter was 30 litre min^{-1}.

Penetration values ranged from 0.01% to 13.7% (Fig. 3) and were greater than the penetration values measured using bacteria and viruses,[2] as expected. As in the previous study,[2] the penetration values of the pleated hydrophobic filters were low compared with all but one of the electrostatic filters (Fig 3) Differences between the BSF were of the same order of magnitude as measured previously when expressed in log$_{10}$ penetration values. However, the clinical relevance of these differences has yet to be established.

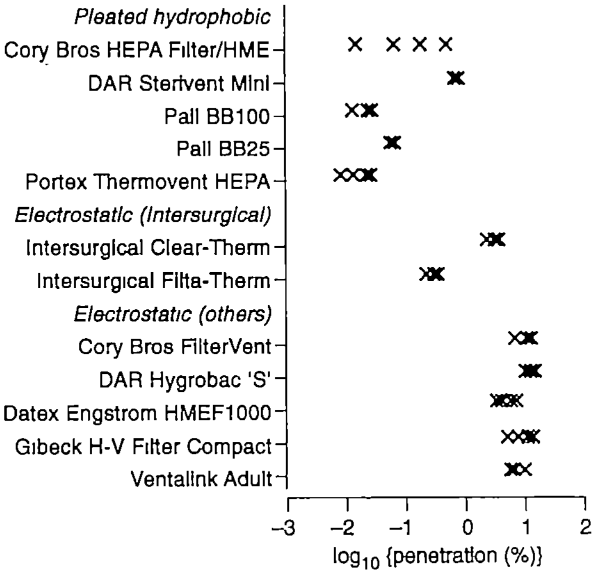


Fig 3 Penetration values of pleated hydrophobic and electrostatic breathing system filters

The standard for respiratory protective devices may provide a useful basis for the development of a standard method for testing BSF.

Keywords. equipment, filters; equipment, breathing systems

Acknowledgement

We thank 3M, Breda, Holland, for the loan of test equipment and technical assistance

References

1 National Institute for Occupational Safety and Health (NIOSH) *Respiratory Protective Devices. Code of Federal Regulations, Title 42, Part 84* (http://www.cdc.gov/niosh/homepage.html)
2 Wilkes AR, Benbough JE, Speight SE. *Br J Anaesth* 1999, **82** 461–2P

Table 12 Effect of various factors on the penetration of salt particles through the two types of breathing system filters (BSF) (– = inconclusive effect)

BSF type	↑Flow	↑Charge on particle	Repeat tests	↑Filter thickness	Conditioning 38°C, 85% RH	Conditioning Simulated clinical use
Electrostatic	↑	↓	↑	↓	–	–
Pleated hydrophobic	↑	–	↓	–	–	–

Factors affecting the filtration performance of breathing system filters

A. R. Wilkes

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, UK

Test equipment is available commercially to assess the filtration performance of respiratory protective devices (AFT 8130, TSI Inc., St. Paul, USA), according to the relevant standard.[1] With a minor modification, the test equipment can be used to measure the filtration performance of breathing system filters (BSF). The apparatus generates salt particles with a mass median aerodynamic diameter of 0.26 µm (assumed to be the most penetrating particle size for the BSF) and measures penetration through the BSF using laser photometers.

Penetration through 42 different examples of BSF was measured to determine the effect of various factors and parameters on filtration performance: flow through the BSF, electrostatic charge on the salt particles, repeated testing (effect of five tests on the same sample), variation in the resistance to gas flow through different samples of the same filter (assumed to represent variations in the thickness of the filter layer) and conditioning of the BSF using either the method described in the standard for respiratory protective devices[1] (maintaining the BSF at 38°C, 85% RH for 25±1 h) or simulated clinical use for 24 h.

Using the same test conditions, penetration values for different BSF ranged from less than the limit of sensitivity of the test equipment (0.001%) to approximately 40%, so that some BSF allow more than 40 000 times more particles through than others under the same test conditions. The effect of some of the parameters and factors was different for the two types of filters tested (electrostatic and pleated hydrophobic) (Table 12), but generally confirmed the theory.

Test equipment intended to test compliance of devices with the standard for respiratory protective devices provides a useful technique for assessing the performance of BSF.

Keywords: equipment, filters; equipment, breathing systems

Acknowledgement

We thank 3M, Breda, Holland, for the loan of test equipment and technical assistance

Reference

1 National Institute for Occupational Safety and Health (NIOSH). *Respiratory Protective Devices. Code of Federal Regulations, Title 42, Part 84* (http://www.cdc.gov/niosh/homepage.html)

Comparison of morphine and pethidine administered by patient-controlled analgesia systems for postoperative pain relief after large bowel anastomosis

P. Armory[1]*, L. Toogood[2]*, M. Thomas[3]*, A. R. Aitkenhead[1] and G. Smith[2]

[1]University Department of Anaesthesia, Queen's Medical Centre, Nottingham, UK. [2]University Department of Anaesthesia, Leicester Royal Infirmary, Leicester, UK [3]Department of Surgery, Leicester General Hospital, Leicester, UK

The incidence of breakdown of a large bowel anastomosis after left-sided colonic resection is up to 20% Mortality in patients whose anastomosis has dehisced is high, management in an intensive therapy unit (ITU) is frequently required and in survivors, duration of hospital stay is greatly extended. There is evidence that analgesic drugs used in the perioperative period may have a significant influence on anastomotic disruption. A randomized, prospective study[1] comparing morphine and pethidine administered after operation by intermittent i.m. injection showed that the risk of anastomotic breakdown was much higher when morphine was given. In this study, we attempted to identify if the risk was altered if the drugs were administered i.v. using patient-controlled analgesia (PCA) systems.

Patients undergoing left-sided colonic resection and anastomosis were identified in five hospitals in Nottingham or Leicester. Each patient was allocated randomly to receive either morphine or pethidine in the perioperative period. The opioid was administered by i.v. injection as required during surgery and in the recovery room, and then by PCA (morphine bolus dose 1 mg, pethidine bolus dose 10 mg; lockout time 5 min) until there was no need for opioid analgesia. Anastomotic breakdown was detected clinically or by Gastrografin enema, if indicated.

Over a 2-yr period, 234 patients were recruited to the study; 116 received morphine (mean age 65.6 (SD=11.1) yr; weight 74 0 (SD 14.7) kg; total perioperative dose 165 (88) mg, male:female ratio 69:47) and 118 received pethidine (age 64.8 (SD=11 1) yr; weight 71.8 (12.6) kg; total perioperative dose 1587 (757) mg; male:female ratio 64:54). There were no differences between groups in preoperative haemoglobin concentration, intraoperative or postoperative blood transfusion, or grade of surgeon who performed the operation. Neostigmine was used to reverse residual effects of a neuromuscular blocking agent in 106 patients who received morphine and in 104 patients who received pethidine. Anastomotic dehiscence occurred in five patients (4.3%) who received morphine and in eight (6.8%) who received pethidine (P=0.41). Two of these patients required admission to the ITU and a third patient died; among the survivors, discharge was delayed by a mean of 12 days.

We conclude that the risk of anastomotic breakdown is not increased when morphine rather than pethidine is given i.v. in the postoperative period using a PCA system in patients who have undergone left-sided colonic resection.

Keywords: surgery, gastrointestinal; complications, anastomotic breakdown; analgesics opioid, morphine; analgesics opioid, pethidine; analgesia, patient-controlled

Acknowledgement

The study was funded in part by a grant from the Association of Anaesthetists of Great Britain and Ireland.

Reference

1 Aitkenhead AR, Robinson S. *Br J Anaesth* 1989; **63**: 230–1P

Monitoring sevoflurane in oxygen using an instrument based on the fluidic bistable amplifier

V. Kulkarni, V. Anderson* and D. G Ross

Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, UK

The fluidic bistable device is a wall attachment amplifier based on the Coanda effect, which is an associated phenomenon of the Venturi effect based on Bernouilli's principle. As the frequency of oscillation of the device is dependent on the density of the fluid flowing through it, it can act as a concentration sensor in binary mixtures containing oxygen and an anaesthetic agent, such as nitrous oxide, halothane, enflurane or isoflurane.[1] ARIGA is an instrument that can measure the frequency of oscillation using PVDF sensors in the feedback control pathway of a fluidic bistable amplifier.[2] The performance of a fluidic bistable device using binary mixtures containing sevoflurane has not been reported previously.

We measured changes in the frequency of oscillation of a fluidic bistable amplifier using ARIGA at increasing concentrations of sevoflurane in oxygen. The anaesthetic circuit included a Manley Pulmovent and the gas mixture was sampled at the junction of the inspiratory and expiratory limbs. The mean of 15 such measurements was plotted against each vaporizer concentration setting. The mean frequency of oscillation decreased from 424 Hz for oxygen to 345 Hz for 8% sevoflurane in oxygen.

There was good correlation between the measurements made by ARIGA and the vaporizer setting (correlation coefficient 0.995) (Fig. 4).

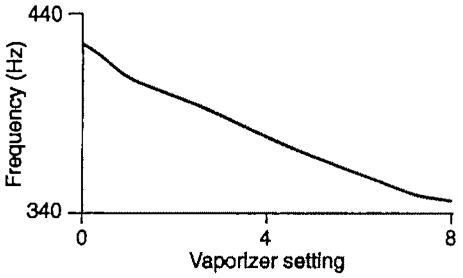


Fig 4 Mean frequency of oscillation at various vaporizer concentrations of sevoflurane in oxygen.

In a binary mixture containing sevoflurane in oxygen, the frequency of oscillation measured by ARIGA can be used to monitor sevoflurane concentration.

Keywords: anaesthetics volatile, sevoflurane; equipment, agent monitor

Acknowledgement

The study was funded by the Aberdeen Royal Hospitals Trust Endowment Funds.

References

1 Rodgers RC, Ross DG. *Br J Anaesth* 1991; **66**: 401–2P
2 Rodgers RC, Kulkarni V, Ross DG, Cana A, Hutchison JMS *Biomed Sci Instrum* 1991; **27**: 311–12

Comparison of two tracheal tube tip designs for oral fibreoptic intubation

R. Greer*, S Smith* and T. Strang*

Department of Anaesthetics, Manchester Royal Infirmary, Manchester, UK

Fibreoptic intubation is a well established technique in anaesthesia where difficult intubation is anticipated. Difficulty in passage of the tube over the fibrescope may be found at the laryngeal inlet, precluding smooth passage of the tube into the trachea. The intubating laryngeal mask airway (Intavent) is supplied with its own tube. The design of the tube tip is different from the standard bevel design. The tip is made from silicone rubber and the angle of the bevel is less marked and slightly tapered. We wished to compare the ease of passage through the laryngeal inlet of the silicone tipped tube compared with the standard bevel design

We studied 30 patients. Patients were anaesthetized with propofol 2–3 mg kg^{-1}, fentanyl 1–2 μg kg^{-1} and atracurium 0.6 mg kg^{-1}. In all cases, oral fibreoptic intubation was attempted We placed a size 10 cm Williams oral intubator in the mouth of the patient. Before the study, patients were allocated randomly to receive either the silicone tipped tube or a size 7.0 armoured tube. The selected tube was railroaded over the fibrescope. The tube was placed on the scope with the bevel facing to the left. The fibrescope was advanced through the cords and into the trachea. At this stage the tip of the scope was in the trachea and the tip of the tube was above the cords. The scope and patient's face were covered with a green towel. A blinded observer passed the tube into the trachea. The tube and scope were then removed and the manoeuvre was repeated using the other type of tube. Again, the blinded observer then passed the tube into the trachea.

We graded the difficulty of passing the tube through the cords: grade 0=no hold up encountered; grade 1=hold up initially relieved by withdrawal and rotation of the tube 90° anticlockwise; and grade 2=hold up requiring more than one manipulation or head movement, or external laryngeal manipulation

McNemar's test confirmed that it was significantly more difficult to pass the armoured tube than the silicone tipped tube (P=0.005) (Table 13).

We conclude that during oral fibreoptic intubation, the silicone tipped tube is easier to pass than the standard tube. This may confer an advantage during fibreoptic intubation.

Keywords: intubation tracheal; intubation tracheal, difficult, equipment, fibrescope

Table 13 Grading of the degree of difficulty of passing the armoured tube and the silicone tipped tube

	Grade 0	Grade 1	Grade 2
Armoured tube	14	8	8
Silicone tipped tube	27	3	0

Effect of interleukin-10 on regulation of NFκB and IκB in an endotoxin rat model

R. L. Paterson, H F Galley, A. E. LeCras and N. R. Webster
Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, UK

Nuclear factor κB (NFκB) is an intracellular transcription factor which regulates genes for several inflammatory mediators implicated in sepsis. Activation of NFκB occurs in leucocytes from patients with sepsis It is retained in an inactive form complexed with its inhibitory subunit IκB, which dissociates from NFκB during the activation process. Activation occurs in response to many stimuli, such as endotoxin or lipopolysaccharide (LPS), resulting in mRNA expression, including IκB mRNA. NFκB is inhibited *in vitro* by interleukin-10 (IL-10), possibly through stabilization of IκB, but the *in vivo* effects of IL-10 are not known. We investigated the effect of IL-10 on NFκB and IκB in endotoxic rats

Female rats were anaesthetized with isoflurane. A tracheostomy was performed and a femoral vein cannulated. The lungs were ventilated to maintain normocapnia. Groups of six rats were allocated randomly to receive LPS 10 mg kg^{-1} i.v. as a bolus and then saline 12 ml kg^{-1} h^{-1}, LPS with IL-10 5 u. kg^{-1} h^{-1} i.v. or saline 12 ml kg^{-1} h^{-1}. The ECG was also monitored. After 3 h the abdomen was opened and the lungs and heart perfused *in situ* with saline. Rats were then killed and the heart, lungs, kidney and liver removed. Tissues were crushed under liquid nitrogen and homogenized in the presence of protease inhibitors. Nuclear proteins were extracted by hypotonic lysis and NFκB activation was determined using the electrophoretic mobility shift assay using ^{32}P-labelled specific oligonucleotides. IκB was measured in cell cytoplasm using western blotting with enhanced chemiluminescence detection. Autoradiographs were quantified by densitometry and expressed in terms of standardized protein loading. Raw data were compared using Kruskal–Wallis and Mann–Whitney *U* testing, as appropriate.

NFκB was detectable in all tissues and increased significantly compared with saline control rats only in the lungs of LPS treated rats ($P<0.05$). IκB was also detectable in all tissues and decreased significantly in the lungs of rats which received LPS ($P<0.05$). In rats that received LPS and IL-10, NFκB was increased further compared with rats treated with LPS alone ($P=0.0104$). IκB remained decreased in the lungs (Fig 5).

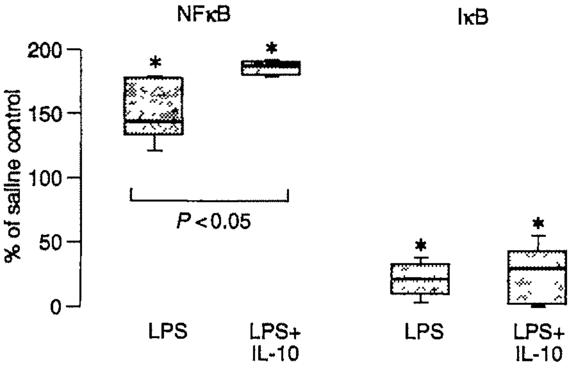


Fig 5 NFκB and IκB in the lungs of rats treated with LPS or LPS and IL-10, as a percentage of expression in saline control rats. Box and whisker plots show median, 25th and 75th percentiles and range *Significantly different from saline control ($P<0.05$) (raw data).

We have shown that NFκB activation occurred in LPS treated rats, associated with decreased expression of IκB, principally in the lungs. However, infusion of IL-10 caused an increase in NFκB, which was not reflected by a further decrease in IκB.

Keywords: blood, nuclear factor kappa B; polypeptides, cytokines; rat

Effect of a single amino acid on the general anaesthetic sensitivity of the strychnine-sensitive glycine receptor

C. J. Weir*[1,2], G. Cabras*[1], K. McGurk*[1], D. Belelli*[1], J. A W Wildsmith[2], J A. Peters*[1] and J. J. Lambert*[1]
[1]*Department of Pharmacology and Neuroscience and* [2]*Department of Anaesthesia, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK*

GABA$_A$ and strychnine-sensitive glycine receptors are putative targets for general anaesthetics. The effect of some anaesthetics on these receptors is dependent on the nature of a single amino acid within a region of the receptor contributing to the chloride ion channel (transmembrane domain 2; TM2). For the homomeric α_1 glycine receptor, the volume of the critical residue is negatively correlated with enhancement of receptor function by ethanol.[1] Here we compare the actions of propofol, pentobarbital and trichloroethanol (TCE) on wild type (WT) glycine α_1 receptors with their effects on receptors where the TM2 serine (270) residue is replaced by the small amino acids glycine (α_1S270G) or alanine (α_1S270A).

Xenopus laevis oocytes were intranuclearly injected with cDNA encoding WT or mutant α_1 subunits and 2–12 days thereafter currents evoked by glycine at EC$_{10}$ were recorded under voltage clamp.[2] The anaesthetic was pre-applied for 60 s before co-application with the agonist. From such experiments, the anaesthetic Emax (amplitude of the response to a maximally effective concentration of anaesthetic expressed as a percentage of the maximal effect of glycine) and the EC$_{50}$ (concentration of anaesthetic producing half-maximal enhancement) were determined. All observations are based on a minimum of three oocytes.

As described previously,[2] propofol, pentobarbital and TCE potentiated, in a concentration-dependent manner, glycine (EC$_{10}$)-evoked currents at the WT type α_1 homomeric receptor. The anaesthetics were similarly effective at glycine α_1 S270G and α_1 S270A receptors, with the exception of pentobarbital which exhibited a reduced maximum at the latter receptor (Table 14) In the absence of glycine, high concentrations of propofol ($\geq$300 μmol litre^{-1}) and TCE ($\geq$10 mmol litre^{-1}), but not pentobarbital, directly activated the WT receptor. The α_1 S270A mutation was associated with enhanced activation by both propofol and TCE, whereas the α_1 S270G substitution increased only the direct effect of propofol. Hence substitution of the TM2 serine by the small amino acids glycine and alanine had little effect on the modulatory action of these anaesthetics but altered the direct gating properties of both propofol and TCE.

Keywords: theories of anaesthesia action, molecular; receptors, glycine

Acknowledgement

Supported by a *BJA* research fellowship (C. J. W.) and MRC (D. B.).

References

1 Ye Q, Koltchine VV, Mihic SJ, *et al. J Biol Chem* 1998; **273**: 3314–19
2 Pistis M, Belelli D, Peters JA, Lambert JJ *Br J Pharmacol* 1997; **122**: 1707–19

Table 14 Mean (SEM) EC_{50} (µmol litre^{-1}) and Emax values for propofol, pentobarbital and trichloroethanol (TCE) on wild type (WT) glycine α_1 receptors and their effects on receptors where the TM2 serine (270) residue was replaced by the amino acids glycine (α_1S270G) or alanine (α_1S270A)

	GLYα_1WT		GLYα_1S270A		GLYα_1 S270G	
	EC_{50}	Emax (%)	EC_{50}	Emax (%)	EC_{50}	Emax (%)
Propofol	16 (3)	85 (5)	21 (0.3)	94 (4)	28 (3)	75 (3)
Pentobarbital	845 (66)	71 (2)	785 (230)	32 (3)	992 (46)	55 (9)
TCE	4129 (252)	77 (10)	2457 (54)	99 (3)	5121 (265)	86 (3)

Effect of xenon on transmission along the somatosensory pathway in the urethane anaesthetized rat

A. Angel

Centre for Research in Anaesthetic Mechanisms, Department of Biomedical Science, The University, Sheffield S10 2TN, UK

It has been shown previously that the majority of anaesthetic agents diminish sensory experience by blocking the transfer of sensory information via the thalamic relay nuclei.[1] In a similar manner, medetomidine disperses and attenuates thalamic sensory transfer.[2] Etomidate and propofol block the transfer of sensory information in the cerebral cortex, showing little effect at the thalamic level.[3] We asked the question, at which site, or sites, along the sensory pathway does xenon exert its action.

Evoked cortical responses and single cell responses along the somatosensory pathway were recorded in rats anaesthetized with urethane 1.25 g kg^{-1}. The animals were allowed to breathe oxygen spontaneously for at least 1 h before administration of 10, 20, 40, 60 and 80% xenon to obviate the problem of xenon–nitrogen exchange.

In common with most other anaesthetic agents, xenon caused a dose-dependent increase in the latency (L) of averaged evoked cortical responses to supramaximal percutaneous electrical stimulation at the wrist (1 s^{-1}) and a decrease in the amplitudes of their initial positive (Pi) and negative waves (Ni). Expressing the results as a change from starting levels to the plateau effect of 80% xenon gave mean changes in L from 0 (SEM 0.23) to 1.10 (0.38) ms; in Pi from 100 (11.74) to 62.89 (22.47)% and in Ni from 100 (53.24) to 13.39 (8.11)%, respectively. All of these changes were statistically significant (paired t test $P<0.05$; $n=8$). For single cells along the somatosensory pathway, the changes in median latency (Lm; ms) and probability (P; %) of discharge were, for control compared with 80% xenon: cuneate (Cu, $n=12$) cells LmCu from 0 (0.15) to −0.15 (0.33), PCu from 100 (3.6) to 88.0 (26.7); for thalamic cells (VPL, $n=4$) LmVPL from 0 (0.11) to 0.33 (0.54), PVPL from 100 (6.8) to 45.0 (27.1) (significantly different from controls); for cortical cells in lamina IV (CoIV, $n=5$) LmCoIV from 0 (0.29) to 0.56 (0.5), PCoIV from 100 (8.9) to 16.6 (13.2) (significantly different from controls); and for cortical cells in lamina V (CoV, $n=8$) LmCoV from 0 (0.35) to 2.35 (2.2) (significantly different from controls), PCoV from 100 (7.3) to 29.2 (20.5) (significantly different from controls), respectively.

These data suggest that xenon exerts its sensory deprivation action by impeding transmission through the thalamic relay nucleus. There is, however, one difference in the action of xenon compared with most other anaesthetic agents in that there is apparently no extra suppression of the probability of responsiveness in cortical layer V cells, although these cells show a large increase in response latencies.

Keywords: anaesthetics gases, xenon; rat

Acknowledgement

We thank BOC for donating the xenon used in this study

References

1 Angel A. *Exp Physiol* 1991, **76**: 1–38
2 Angel A, Arnott RH, Wolstenholme SC In: Daniels S, Smith EB, eds *Gases in Medicine; Anaesthesia, 8th BOC Priestley Conference*. Cambridge: Royal Society of Chemistry, 1998; 53–85
3 Angel A, Arnott RH. *Eur J Neurosci* 1999, **11**: 2497–505

Effect of systemic bicuculline on sensory transmission in the urethane-anaesthetized rat

R. H. Arnott and **A Angel**

Centre for Research into Anaesthetic Mechanisms, Department of Biomedical Science, University of Sheffield, Western Bank, Sheffield, UK

Recent molecular biological studies have suggested that potentiation of γ aminobutyric acidergic (GABAergic) transmission may have an important role in the mechanism of general anaesthetic action.[1] We examined this hypothesis by measuring the effect of systemic administration of bicuculline methiodide, a $GABA_A$ receptor antagonist, on evoked responses in the dorsal column medial lemniscal pathway. Changes in these responses have been shown to provide an index of depth of anaesthesia.[2]

Five female Wistar rats, weighing 190–210 g, were anaesthetized by i.p. injection of urethane 1.25–1.5 g kg^{-1}, without premedication. The rats were surgically prepared for recording cellular behaviour in the dorsal column pathway, as described previously.[2] Sensory afferent impulses were evoked, once a second, by supramaximal electrical stimulation of the forepaw. Mass responses were recorded from the cortical surface; cellular responses were recorded from single ventroposterolateral thalamic cells via stereotaxically placed glass microelectrodes After a 500-s period of control recording, bicuculline methiodide dissolved in 0.9% saline was administered i.p. to provide doses of 0.1, 1.0 and 10 mg kg^{-1} at successive 500-s intervals. These doses were chosen because systemic bicuculline 2 mg kg^{-1} has been shown to cause electrocortical seizure activity in anaesthetized cats.[3]

Bicuculline did not significantly alter the latency of ventroposterolateral thalamic cellular or cortical mass responses to peripheral stimulation. At the highest dose, bicuculline caused a significant increase in the normalized probability of thalamic cellular response (from mean 100 (SEM 1.2)% to 115 (4)%, $P<0.05$, Student's paired two-tailed t test). There was no significant change in the amplitude of the initial positive inflection in the cortical mass response nor was there any significant alteration in the initial negative inflection, except at the 1 mg kg^{-1} dose where the normalized amplitude was significantly increased from 100 (4) to 169 (18)% ($P<0.05$, Student's paired two-tailed t test).

In comparison with the large alterations in sensory transmission which are associated with administration of anaesthetics,[2] bicuculline caused only limited changes in responsiveness in the dorsal column pathway. While these data provide some support for the suggestion of GABAergic involvement in the anaesthetic process, they do not provide the compelling evidence which would be expected from block of a wholly GABAergic process. Future work will investigate the effect of bicuculline on corticothalamic modulatory processes and on the effects of etomidate, a drug most recently suggested to have a GABA modulatory mode of action.

Keywords. receptors, amino acid; brain, GABA; monitoring, evoked potentials; rat

References

1 Lambert JJ, Belelli D, Shepherd S, Muntoni AL, Pistis M, Peters JA. In: Smith EB, Daniels S, eds. *Gases in Medicine: Anaesthesia*. Cambridge: Royal Society of Chemistry, 1998; 121–37

2 Angel A. *Exp Physiol* 1991; **76**: 1–38

3 Neckelmann DAG, Amzica F, Steriade M. *J Neurophysiol* 1998; **80**: 1480–94.

Methylene blue and immune activation in ischaemia reperfusion injury

J. A. Gedney, H Koelzow, J. Baumann* and M. C. Bellamy

Intensive Care Unit, St James's University Hospital, Leeds, UK

The dye methylene blue (MB) has been used both as an antioxidant and a nitric oxide blocking agent. We have previously reported its effect in attenuating haemodynamic changes of ischaemia reperfusion syndrome in human orthotopic liver transplantation (OLT). This was mediated primarily by inhibition of cGMP. We report changes in inflammatory mediators and white cell activation in these patients.

We studied 36 patients undergoing OLT. All patients received a standardized anaesthetic. Patients were allocated randomly to receive MB 1.5 mg kg^{-1} or an equivalent volume of normal saline i.v. by rapid bolus, 1 min before graft reperfusion. IL-8 and IL-10 were assayed by ELISA, 5 min before and 5 and 60 min after graft reperfusion We measured monocyte HLA-DR expression and neutrophil CD11b expression by flow cytometry. Total plasma nitrite–nitrate was assayed by the Griess reaction and cGMP by immunoassay. Results are expressed as mean (SEM). Comparisons were made by Student's *t* test and two-way ANOVA, as appropriate.

IL-8 increased in controls from 37 (8) to 128(27) pg ml^{-1} and in the MB group from 22 (6) to 124 (16) pg ml^{-1}. Similarly, IL-10 increased from 12 (3) to 732 (127) pg ml^{-1} in controls and from 10 (2) to 768 (75) pg ml^{-1} in the MB group. The trends in both cytokines were highly significant with time ($P<0.0001$) but there were no differences between the MB and control groups. Monocyte HLA-DR expression did not change in either group. There was no correlation between IL-10 and HLA-DR expression. Neutrophil CD11b expression was higher in the MB group than in controls (Fig. 6).

After hepatic ischaemia reperfusion injury, the haemodynamic improvement seen with administration of MB is unrelated to concentrations of cytokine. In most models of injury, there is a negative correlation between IL-10 and HLA-DR expression. We failed to observe this correlation. Neutrophil CD11b expression was greater in the MB group compared with controls. This may relate to direct effects of MB on the neutrophil; inhibition of cGMP could block anti-inflammatory effects of nitric oxide. The clinical relevance of this observation is unknown.

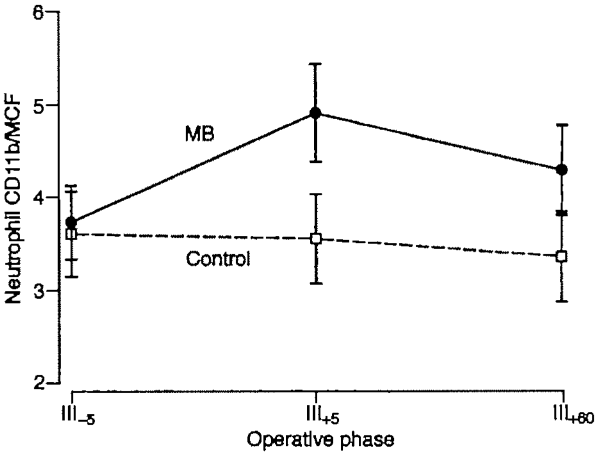


Fig 6 Neutrophil CD11b expression in the methylene blue (MB) group and in controls during orthotopic liver transplantation. $P<0.05$ MB compared with control (whole curves).

Keywords: pharmacology, methylene blue; liver, transplantation; polypeptides, cytokines; blood, neutrophils

Analgesic action of nitrous oxide is transduced by alpha-$_2$B adrenergic receptors and enkephalin release in rodents

M. Maze*, M. Fujinaga*, G Tianzhi*, F. Davies* and A. Zimmer*

Department of Anesthesia, Stanford University and the Anesthesiology Service (112A), VAPAMC, USA

For the first 150 yr after the introduction into clinical practice, anaesthesia was considered to be produced through non-specific perturbations of lipids. In the past decade, a series of seminal discoveries by Professor Franks and Dr Lieb indicated that anaesthesia is transduced at specific sites on a relatively small number of proteins. Our programme focuses on the mechanisms whereby α_2 adrenoceptors and their transmembrane signalling, in defined neuronal pathways, produce anaesthesia and analgesia, both in response to direct activation by exogenously administered α_2 agonists (such as dexmedetomidine) and by indirect activation via release of the endogenous α_2 ligand norepinephrine (as is the case with nitrous oxide analgesia). We now report on the mechanism of the analgesic action of nitrous oxide.

Using the tail-flick latency response, we have shown that systemically administered antagonists of opioid (naloxone) and α_2 adrenergic (yohimbine, atipamezole) receptors block its antinociceptive action. This is a result of opioid receptors in the periaqueductal gray and α_2 adrenoceptors in the spinal cord. As spinal cord transection blocks the analgesic properties of nitrous oxide, a descending pathway is involved. At the level of the dorsal horn of the spinal cord, nitrous oxide provokes the release of norepinephrine. The released norepinephrine is responsible for analgesia as depletion of spinal stores of this neurotransmitter blocks the analgesic action of nitrous oxide. Using genetically modified reagents, we have now identified the species of endogenous opioid ligand and the α_2 adrenoceptor involved. PENK 2 mice which lack preproenkephalin (the precursor of enkephalin) have no analgesic effect to nitrous oxide. Also, mice which lack the α_2B adrenoceptor subtype also have no analgesic action to nitrous oxide (Fig. 7). The analgesic action of nitrous oxide could also be blocked by prazosin, an antagonist of the α_2B adrenoceptor subtype. Both PENK 2 and α_2 adrenoceptor subtype knockout mice have normal anaesthetic (hypnotic) responses to nitrous oxide.

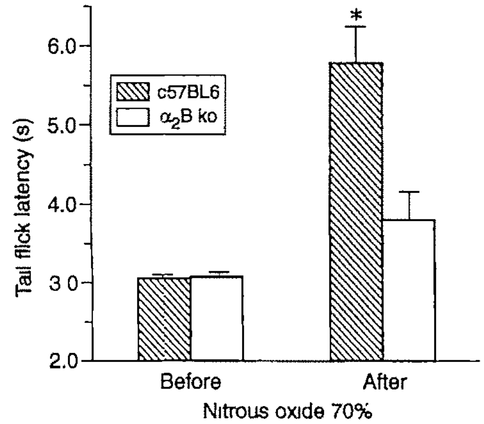


Fig 7 Nitrous oxide does not exert analgesic effects in mice lacking the α_2B adrenoceptor subtype.

In summary, nitrous oxide produces its analgesic mechanism via different neuronal pathways (descending spinal noradrenergic) and molecular mechanisms (α_2B adrenoceptor in the spinal cord and release of enkephalin in the periaqueductal grey) than that for transduction of its anaesthetic response (NMDA receptor).

Keywords: pain, mechanism, anaesthetics gases, nitrous oxide; receptors, adrenergic; polypeptides, enkephalins

Fentanyl disposition in anaesthetized patients with renal failure using an iodine-labelled RIA

J. W. Sear and C W Hand*

Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

Although the disposition of i.v. bolus doses of fentanyl in patients with renal failure has been reported elsewhere,[1] no parameter estimates were given, other studies have not compared renal failure patients with controls. In this study, we have measured plasma fentanyl concentrations using an iodine-labelled RIA. Ten patients undergoing renal transplantation (aged 18–66 yr; weight 30–79.6 kg) and nine healthy patients undergoing abdominal surgery (aged 39–65 yr, weight 57–85.6 kg) received an i.v bolus dose of fentanyl as part of a balanced anaesthetic technique Patients with renal failure underwent dialysis before anaesthesia and surgery, and preoperative plasma creatinine and urea concentrations were recorded. All patients continued their intercurrent medication until premedication.

After premedication with a benzodiazepine, anaesthesia was induced with thiopental. After neuromuscular block, patients' lungs were ventilated to normocapnia with an inspired gas mixture of 66% nitrous oxide in oxygen supplemented by a volatile agent Fentanyl 200–650 µg was given i.v. over 30 s, and blood samples collected from a venous cannula in the contralateral arm at times to 360 min Plasma was separated by centrifugation, and fentanyl concentrations measured using an ^{125}I-labelled solid-phase RIA[2] (DPC Coat-a-Count) The assay had coefficients of variation of 4.2% and 10.4% at concentrations of 5.5 ng ml^{-1} and 0.65 ng ml^{-1}, respectively, and a limit of detection of 0.04 ng ml^{-1} Plasma concentration–time data were used to determine area under the curve (AUC) and area under the first moment curve (AUMC), mean residence time (MRT), plasma clearance (*Cl*p) and apparent volume of distribution at steady state (V^{ss}). Results are shown in Table 15.

There was considerable intra-subject variation in the two groups, data for the healthy patients were in agreement with Peng and Sandler.[3] Similarly, data for the renal transplant patients reflected the range of values reported elsewhere for patients with renal impairment,[4] and were not significantly different from healthy controls. In contrast with Koehntop and Rodman, we found no relationship between preoperative plasma urea or creatinine concentrations and fentanyl clearance in uraemic patients

Keywords: analgesics opioid, fentanyl; pharmacokinetics, fentanyl; kidney, failure, kidney, transplantation

References

1 Corall IM, Moore AR, Strunin L *Br J Anaesth* 1980; **52**· 101P
2 Watts VW, Caplan YH. *J Anal Toxicol* 1990, **14**. 266–72
3 Peng PWH, Sandler AN. *Anesthesiology* 1999; **90** 576–99
4 Koehntop DE, Rodman JH *Pharmacotherapy* 1997, **17** 746–52

Table 15 Mean (SD) plasma clearance (*Cl*p), mean residence time (MRT) and apparent volume of distribution at steady state (V^{ss}) in the renal transplant and healthy patients

	n	*Cl*p (ml min^{-1})	MRT (min)	V^{ss} (litre)
Renal failure	10	1212.3 (667 7)	228 4 (179 3)	236 8 (158 8)
Healthy patients	9	1293.9 (627 2)	175 0 (85 5)	207 3 (127 3)

POSTER PRESENTATIONS

The transient hyperaemic response in healthy pregnant patients compared with non-pregnant controls

R. A. Bowie, M. M E Henfrey*, R Sherman* and R P Mahajan

University Department of Anaesthesia, Nottingham City Hospital, Nottingham, UK

Pregnancy is associated with widespread changes in vascular tone and reactivity.[1] Cerebral blood flow has been shown to be increased in pregnancy[2] but it is not known if this is associated with changes in cerebral autoregulation. The transient hyperaemic response (THR) in the middle cerebral artery (MCA) flow velocity (vmca) after release of a brief compression of the ipsilateral common carotid artery has been used to assess cerebral autoregulation [3] The THR ratio (THRR) and strength of autoregulation (SA) have been described as indices of cerebral autoregulation [4] We used the THR test in healthy pregnant patients and a matched group of

Table 16 Mean (SD) end-tidal carbon dioxide concentration (E'_{CO_2}), flow velocity in the middle cerebral artery (*v*mca), mean arterial pressure (MAP), compression ratio (CR), the transient hyperaemic response ratio (THRR) and strength of autoregulation (SA) in pregnant patients and a matched group of non-pregnant volunteers. ****P*<0.001

	Non-pregnant (*n*=30)	Pregnant (*n*=30)
E'_{CO_2} (kPa)	5.1 (0.4)	4.2 (0.4)***
*v*mca (cm s^{-1})	68.27 (14.53)	56.65 (11.48)***
MAP (mm Hg)	87 (8)	86 (10)
CR	34.8 (12.2)	29.7 (8.0)
THRR	1.56 (0.26)	1.64 (0.19)
SA	1.13 (0.20)	1.21 (0.19)

non-pregnant volunteers to assess the effect of pregnancy on cerebral autoregulation.

We recruited 30 healthy pregnant patients (aged 18–41 yr) in their third trimester from the antenatal clinic and an age- and height-matched non-pregnant control group. The study set-up included transcranial Doppler ultrasonography for continuous measurement of *v*mca, end-tidal carbon dioxide concentration (E'_{CO_2}) and non-invasive measurement of mean arterial pressure (MAP). The THR test was performed by compression of the ipsilateral common carotid artery for 10 s. The time-averaged mean of peak *v*mca for the waveforms just before compression (F1), just after compression (F2) and just after release of compression (F3) were selected. The magnitude of the decrease in *v*mca at the onset of compression (compression ratio (CR)) was calculated as (F1–F2)×100/F1. THRR was calculated as F3/F1. MCA perfusion pressure during compression (P2) was estimated as F2/F1×MAP. SA was calculated as (F3×P2)/(F1×MAP). If the estimated value of P2 was less than 60 mm Hg, a nominal value of 60 mm Hg was used in the calculation of SA. Data were analysed using unpaired Student's *t* tests.

Our results showed that the pregnant group had significantly lower values for both E'_{CO_2} and *v*mca compared with the matched control group (Table 16). However, there was no difference in cerebral autoregulation, as assessed by the calculated indices of THR.

Keywords: brain, blood flow; pregnancy

References

1 Kim TH, Winer CP, Thompson LP. *Am J Physiol* 1994; **267**: 41–7
2 Ikeda T, Ikenoue T, Mori N. *Am J Obstet Gynecol* 1993; **168**: 1303–8
3 Smielewski P, Czosnyka M, Kirkpatrick P, McEroy H, Rutkowska H, Pickard JD. *Stroke* 1996; **27**: 2197–203
4 Mahajan RP, Cavill G, Simpson EJ. *Anesth Analg* 1998; **87**: 843–9

Comparison of the effects of remifentanil and alfentanil on the cardiovascular response to orotracheal intubation in treated hypertensive patients

A. M. Maguire*, J. P Thompson, N. Kumar and D. J. Rowbotham
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester, UK

Few studies of the cardiovascular response to intubation have been carried out in high-risk patients.[1] In this study, we have compared the relative efficacy of remifentanil and alfentanil in modifying the cardiovascular response to intubation in a group of patients receiving long-term treatment for hypertension (>6 months).

In a randomized, double-blind study, 40 ASA II–III patients were allocated to receive remifentanil 0.5 μg kg^{-1} followed by an infusion of 0.1 μg kg^{-1} min^{-1} or alfentanil 10 μg kg^{-1} followed by an infusion of saline. Glycopyrrolate 200 μg was administered to all patients before the study drug. Anaesthesia was induced with propofol, rocuronium and 1% isoflurane with 66% nitrous oxide in oxygen. Laryngoscopy and tracheal intubation were performed 3 min after induction. Heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were recorded at 1-min intervals from preoxygenation until 5 min after intubation. Escape medication for hypotension, hypertension or bradycardia was administered as required. Data were analysed using multivariate analysis of variance for repeated measures, and paired and unpaired *t* tests, as appropriate Power analysis, using data from a previous study,[2] showed that 20 patients in each group were required to detect a difference in MAP of 15 mm Hg between groups ($\alpha=0.05$, $\beta=0.2$).

MAP and HR increased after laryngoscopy and intubation in both groups, but there were no significant differences between the remifentanil and alfentanil groups at any time (Table 17). Seven patients in the remifentanil and four in the alfentanil groups required ephedrine (3–16 mg) to treat hypertension (SAP <100 mm Hg)

We found that the effect of remifentanil 0.5 μg kg^{-1} followed by an infusion of 0.1 μg kg^{-1} min^{-1} was similar to that of a bolus dose of alfentanil 10 μg kg^{-1} in attenuating the cardiovascular response to intubation in treated hypertensive patients.

Keywords: analgesics opioid, remifentanil; analgesics opioid, alfentanil; cardiovascular system, effects; intubation tracheal; complications, hypertension

References

1 Thomson IR *Can J Anaesth* 1989; **36**: 367–9
2 Thompson JP, Hall AP, Cagney B, Rowbotham D. *Br J Anaesth* 1998, **80**: 467–9

Table 17 Mean (SD) mean arterial pressure (MAP) and heart rate (HR) in the remifentanil and alfentanil groups. **P*< 0.05 compared with pre-intubation

			Time after intubation		
Group	**Pre-induction**	**Pre-intubation**	**1 min**	**3 min**	**5 min**
Remifentanil					
HR (beat min^{-1})	75 (14)	72 (14)	87 (12)*	79 (12)*	75 (14)
MAP (mm Hg)	106 (19)	74 (18)	100 (17)*	84 (17)*	74 (15)
Alfentanil					
HR (beat min^{-1})	74 (12)	70 (15)	89 (19)*	82 (15)*	79 (15)*
MAP (mm Hg)	111 (15)	72 (21)	105 (32)*	98 (16)*	86 (19)*

Iontophoretically applied lidocaine to prevent pain associated with injection of i.v. propofol: comparison with i.v. lidocaine

P. Sharpe*, M. Asif*, A. Victoria*, R. Vaja* and D. J. Rowbotham

University Department of Anaesthesia and Pain Management, Leicester Royal Infirmary, Leicester, UK

Pain after injection of propofol is a common clinical problem, with an incidence of up to 90%.[1] Lidocaine 40 mg can reduce the incidence of pain to approximately 13%.[1] Iontophoresis delivers charged drugs, such as lidocaine, via application of a small electrical current.[2,3] We have shown that iontophoresis reduces the pain associated with propofol injection.[3] However, there have been no comparative studies. Therefore, we have compared iontophoresis of 4% lidocaine 1.5 ml with lidocaine 40 mg mixed with propofol. Patients (n=60) were allocated randomly to one of two groups. Group 1 received sham iontophoresis followed by propofol mixed with lidocaine 40 mg and group 2 received iontophoresis of 4% lidocaine 1.5 ml followed by injection of propofol mixed with normal saline 2 ml. A current of 4 mA was applied over a vein on the dorsum of the hand for 10 min in the active group. The sham group were treated identically, except that no current was passed. After 10 min, a 20-gauge cannula was sited in both groups. Propofol was injected at a rate of 20 mg every 5 s for a total of 30 s. During administration, pain scores (VAS and categorical) were recorded at 10-s intervals.

Both groups were well matched for age (group 1, median 32 (range 18–71) yr; group 2, 38 (18–71) yr) and sex distribution (M:F (%) 30:70 in group 1 and 40:60 in group 2).

Pain on administration of propofol was significantly greater in the iontophoresis group (Table 18).

Table 18 Pain on administration of propofol in the iontophoresis and lidocaine groups (n=59, one patient in the iontophoresis group was unable to successfully express their pain scores using the verbal assessment tool) *P<0.05 (chi-square test)

	No or mild pain (%)	Moderate or severe pain (%)
Iontophoresis	73.3	26.7*
I.v. lidocaine	93.1	6.9*

Iontophoretic application of 4% lidocaine 1.5 ml did not reduce pain to the same degree as lidocaine 40 mg mixed with propofol.

Keywords. anaesthetics local, lidocaine; anaesthetics i.v., propofol; pain, injection

References

1 Tan CH, Onsiong MK. *Anaesthesia* 1998; **53**: 468–76
2 Costello CT, Jeske AH. *Phys Ther* 1995; **75**: 554–63
3 Sadler PJ, Thompson HM, Maslowski P, Liddle A, Rowbotham DJ. *Br J Anaesth* 1999; **82**: 432–4

Iontophoretic application of methylene blue through porcine skin: influence of polarity

C. Flucker*, P. Sharpe*, P. Maslowski* and D. Rowbotham

University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE5 1WW, UK

Iontophoresis delivers charged molecules through the skin via application of an electrical current. The polarity of the drug and electrode is such that the drug is repelled from the electrode into the tissues. Iontophoresis of lidocaine reduces the pain of cannula insertion and propofol administration.[1] Methylene blue, a basic cationic dye, has similar physicochemical properties to lidocaine and has recently been delivered through porcine skin, an animal model of human skin.[2] This allows direct visualization of drug deposition. During clinical use of iontophoresed lidocaine, it was noted that skin analgesia was achieved, despite application of reverse polarity to the electrode. Therefore, we have investigated the effects of polarity on the penetrance of methylene blue in a porcine skin model.

Freshly excised hair bearing porcine skin was prepared with isopropyl alcohol. Methylene blue 1% (1.5 ml) was applied to the gel electrode placed on the skin. A reference electrode was placed 10 cm distant. Initially, methylene blue was iontophoresed in its usual fashion towards the cathode using an Iomed phoresor II device delivering 4 mAmp for 20 min. A voltmeter was used to check the integrity and performance of the circuit. This was then repeated in an identical manner except that the polarity was reversed so that the gel electrode now became the cathode. Controls were obtained by applying methylene blue electrodes to the skin for 20 min but without application of current. Biopsies were obtained and processed by frozen section.

The control group showed minimal surface staining with methylene blue whereas both normal polarity (cathodal) and reverse polarity (anodal) clearly showed penetrance of methylene blue through the dermis with nuclear staining of subdermal appendages. Staining occurred to a depth of 0.5–0.6 mm with normal polarity and reverse polarity.

Therefore, it appears that polarity has little influence on the iontophoresis of methylene blue through porcine skin under these conditions. We postulate that iontophoretic currents have complex actions on the skin, possibly causing it to become more permeable[3] at clinically relevant dosages. We intend to investigate this effect further using a range of currents to see if any cut-off point occurs below which reverse polarity loses its effect.

Keywords: pharmacology, methylene blue, model, skin, pig

References

1 Sadler PJ, Thompson HM, Maslowski P, Liddle A, Rowbotham DJ. *Br J Anaesth* 1999; **82**: 432–4
2 Johnson PJ, Gallo SA, Hui SW, Oseroff AR. *J Invest Dermatol* 1998, **111**. 457–63
3 Chizmadzhev YA, Indenbom AV, Kuzmin PL, Galichenko SV, Weaver JC, Potts RO. *Biophys J* 1998, **74**: 843–56

Total inhalation anaesthesia *vs* total i.v. anaesthesia: cost comparison of sevoflurane and propofol

T. M. Akhtar, M. W. O. Frow* and J. I. Miranda-Carabello

Queen Mary's Hospital, Frognal Avenue, Sidcup, Kent DA14 6LT, UK

The newer general anaesthetic agents provide more rapid recovery and fewer side effects than older drugs,[1] while being more expensive.[2] We prospectively compared direct and ancillary drug costs of total i.v. anaesthesia with propofol and total inhalation anaesthesia with sevoflurane for induction and maintenance with 50–60% nitrous oxide and a circle breathing system. We studied spontaneously breathing day-case gynaecological patients.

Fifty consecutive, unpremedicated, ASA I or II patients received sevoflurane or propofol at random. Patients received droperidol 1 mg and fentanyl 1 μg kg^{-1}. Induction was achieved by breathing

Table 19 Volume and cost (95% confidence limits) of each drug for general anaesthesia

	Sevoflurane		**Propofol**	
	Volume (ml)	**Cost (£)**	**Volume (ml)**	**Cost (£)**
Induction				
Per patient	4.2 (3.8–4.6)	2.46 (2.21–2.67)	10.8 (9.9–11.8)	2.71 (2.48–2.96)
Maintenance				
Per patient	5.4 (4.1–6.8)	3.15 (2.37–3.93)	65.2 (53.12–77.28)	16.35 (13.32–19.38)
Per minute	0.3 (0.2–0.4)	0.18 (0.13–0.22)	2.94 (2.46–3.49)	0.74 (0.60–0.88)
Combined				
Per patient	9.7 (8.4–11.1)	5.61 (2.04–4.86)	71.7 (58.9–84.5)	17.98 (14.77–21.20)
Per minute	0.6 (0.5–0.7)	0.34 (0.29–0.38)	3.43 (2.92–3.93)	0.86 (0.73–0.99)

a 60:40 mixture of nitrous oxide and oxygen with either a Graseby 3500 Diprifusor set at a target blood concentration of 6 μg ml^{-1} or by vital capacity breathing with an end-inspiratory pause and 8% sevoflurane. After induction, gas flows were reduced to 2 litre min^{-1}, and the anaesthetists continued according to their usual practice. All events were timed.

The volumes of anaesthetic agents used were calculated for induction and maintenance, and costed.[3] Propofol volumes were calculated according to the manufacturer's guidelines to include waste. Sevoflurane volumes were calculated from weight changes of the vaporizer:

Volume=fresh gas flow (litre min^{-1})×weight (kg)×time (min) ×F_I sevo×M_r sevo

24 040 (ml of vapour in 1 mole of gas at RTP)×density sevo (g ml^{-1})

Induction with sevoflurane was not significantly cheaper than propofol (P=0.06–0.07); maintenance was four times cheaper (Table 19). Overall, sevoflurane was 2.5 times cheaper per minute than propofol, despite the shorter mean duration of anaesthesia (18 *vs* 23 min; $P<0.04$). There were no significant differences in induction, 'knife to skin', laryngeal mask removal or post-induction apnoea times, ancillary drug costs (excluding prophylactic antiemetics), pain, nausea and vomiting, sedation or patient satisfaction after operation. In summary, sevoflurane was significantly cheaper than propofol in spontaneously breathing patients.

Keywords: anaesthesia, general; anaesthesia, audit; anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane

Acknowledgement

Supported by Abbott and AstraZeneca.

References

1 Smith I, Nathanson MH, White PF. *Anesth Analg* 1995; **81**: S67–72
2 Rosenburg MK, Bridge P, Brown M. *Anesth Analg* 1994; **79**: 852–5
3 *British National Formulary, No.* 37. March 1999; 547–50

British Journal of Anaesthesia **84** **(2)**: 289–95 (2000)

Correspondence

Post-thoracotomy epidural *vs* paravertebral analgesia

Editor,—I read with interest the article by Richardson and colleagues on post-thoracotomy pain.[1] The authors compared thoracic paravertebral bupivacaine (bolus of 0.5% followed by infusion of 0.5%) with thoracic epidural bupivacaine (bolus of 0.25% followed by infusion of 0.25%). Both groups received PCA morphine. The paravertebral group had significantly lower pain scores, better preservation of respiratory function, lower incidence of chest infections, and less nausea, vomiting and hypotension. Thus the authors concluded that with these regimens, paravertebral block was superior to epidural bupivacaine. As many believe that thoracic epidural can provide superior analgesia, these are impressive findings.

I feel it is important to emphasize that Richardson and colleagues used 0.25% bupivacaine without opioids in the epidural group, which is an uncommon practice. A combination of local anaesthetic and opioid administered epidurally has been shown to be synergistic.[2 3] Even though the optimal drug combination has yet to be determined, 91% of anaesthetists in the UK use a combination of bupivacaine with either fentanyl or diamorphine.[4] Choosing to administer only local anaesthetic epidurally effectively handicapped the epidural group in comparison with the paravertebral group. It is conceivable that a combination of an opioid and dilute 0.1% bupivacaine would have resulted in a significantly better outcome in the epidural group.

The authors reasoned against using a local anaesthetic–opioid combination regimen for the epidural group on the basis that all patients returned to the general ward and they were unsure how to provide additional rescue opioid analgesia, as a combination of neuraxial and systemic opioids (for example) is known to be a major risk factor of respiratory depression. It is worth noting that 39% of respondents to a survey of thoracic epidural analgesia practice allowed patients to return to a general ward without specific additional nursing resources.[4] Inadequate analgesia with a correctly placed epidural catheter can generally be managed with an epidural top-up; systemic opioids are usually not needed. The use of epidural morphine, including top-ups, has been shown to be safe on surgical wards.[5]

Paravertebral analgesia is an attractive alternative to epidural analgesia: it is a relatively easy technique and is free of the risk of major neurological injury. We need a study comparing the two methods of analgesia where each technique is individually optimized. Otherwise I am left wondering whether paravertebral analgesia is really as good or maybe even better than thoracic epidural.

J. Y. Y Wang
Department of Anaesthesia
Edinburgh Royal Infirmary
Edinburgh, UK

1 Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. *Br J Anaesth* 1999; **83**: 387–92

2 Tejwani GA, Rattan AK, McDonald JS. Role of spinal opioid receptors in the antinociceptive interactions between intrathecal morphine and bupivacaine. *Anesth Analg* 1992; **84**. 726–34

3 Mourisse J, Hasenbros M, Gielen M, *et al.* Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain *Acta Anaesthesiol Scand* 1992; **36**: 70–4

4 Romer HC, Russell GN. A survey of the practice of thoracic epidural analgesia in the United Kingdom. *Anaesthesia* 1998; **53**: 1012–27

5 Ready LB, Loper KA, Nessly M, Wild L Postoperative epidural morphine is safe on surgical wards. *Anesthesiology* 1991; **75**: 453–6

Editor,—I am grateful to Dr Wang for the interest in our study. I appreciate the points he has made, but I must try to justify our choice of epidural regimen.

To some extent, better pain relief may have been provided by addition of an opioid to epidural bupivacaine. Pain relief at rest may have been enhanced, but I am doubtful that pain on movement or coughing would have been affected sufficiently to improve pulmonary function (our primary outcome variable). Pain is the most important factor responsible for the post-thoracotomy impairment of pulmonary function[1] and bedside spirometry is a good indicator of the dynamic capabilities of a chosen analgesic regimen.[2] I would argue that to undertake research into thoracic or upper abdominal pain without studying pulmonary function is to render the data of lower quality. Pain scores and opioid requirements, which are often the main study outcome variables, are ‘soft’ data and have little comparative meaning. Pain scores on coughing are better but what exactly is a ‘cough’? Is it clearing of the throat or clearing of lung base secretions? The difference in chest wall movement and hence post-thoracotomy pain exacerbation between these two manoeuvres could be great. I have found only one prospective, randomized study which used a combination of local anaesthetic (bupivacaine) and a opioid (fentanyl) for post-thoracotomy pain and studied spirometric function.[3] Values were reduced to 50–60% of baseline throughout the study, which are inferior to our values using plain epidural bupivacaine.

Opioids are primarily c-fibre inhibitors. In the presence of a large chest wound with severe soft tissue, bony, ligamentous and intercostal nerve damage, pain generation with movement (i.e., with respiration) is probably mediated via intercostal A-delta fibres, although the sympathetic, vagal and phrenic afferents may also be involved.[4] As opioid receptors are absent from these fibres,[5] opioids cannot be expected to provide pain relief with respiration. Administering these drugs by different routes (e g., neuraxially) does not alter their pharmacology. In my view, it disadvantages the postoperative patient (as opposed to the obstetric patient) if use is made of synergy between epidural local anaesthetic and opioid to allow a reduction in the amount of local anaesthetic. From neurophysiological and neuroendocrine perspectives, I subscribe to the view that the greatest block density possible is the essential starting point if outcomes are to be improved. We need to define clearly our postoperative analgesic goals. Is pain relief per se adequate or should we aim to facilitate chest physiotherapy and postoperative pulmonary function? I am sure that only through the latter can we improve outcome.

I do wonder if the analgesia which follows systemic or neuraxial lipophilic opioid administration comes entirely from suppression of sighing and deep breathing, inhibition of the cough reflex and through sedation which attenuates the desire for movement Provocatively, I have put this question to many speakers at

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

scientific meetings and I have not yet received an adequate reply. I would like to be corrected if my information is erroneous. Having made these comments, I am mindful that both of our groups needed additional opioid analgesia and I take this as a spur to continue to refine our regional analgesic techniques.

I agree that thoracic epidural analgesia can be continued on the general ward without additional nursing resources. This is indeed the practice in our own hospital where over the past 8 yr many hundreds of epidurals, using bupivacaine and morphine, have been managed without untoward respiratory incident. To restrict this form of analgesia to only those patients with two to one nursing ratios is a distortion of responsibilities. However, we felt that deviation from this (our standard) practice was necessary for the sake of our study. We had to circumvent any barrier, albeit unwittingly imposed, between the patient and additional analgesia. Additional epidural top-ups could have been given, but this would have involved delay and therefore introduced bias to the detriment of the epidural group and hence our data quality

Obviously, high quality studies are required. The simple question, 'can epidural opioid/local anaesthetic regimes compared with epidural local anaesthetic provide improved post-thoracotomy pulmonary function or improved outcome?' needs to be answered. Further small studies with different combinations examining pain scores and side effects are not helpful. I would be interested in taking the dose regimens from the resulting optimal study and comparing them in our own institution with our paravertebral nerve block based regimen. For ethical reasons, it is not possible for me to try to answer this question myself.

J. Richardson
Department of Anaesthesia
Bradford Royal Infirmary
Bradford, UK

1 Sabanathan S, Eng J, Mearns AJ. Alterations in respiratory mechanics following thoracotomy. *J R Coll Surg Edinb* 1990; **35**: 144–50
2 Richardson J, Sabanathan S, Shah R. Postthoracotomy spirometric lung function: the effect of analgesia A review. *J Cardiovasc Surg* 1999; **40**: 445–56
3 George KA, Wright PMC, Chisakuta A. Continuous thoracic epidural fentanyl for post-thoracotomy pain relief with or without bupivacaine? *Anaesthesia* 1991; **46**: 732–6
4 Sabanathan S, Richardson J, Mearns AJ. Management of pain in thoracic surgery. *Br J Hosp Med* 1993, **50**. 114–20
5 Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth* 1995; **75**: 193–200

Appropriate size of laryngeal mask

Editor,—We read with interest the article by Asai and colleagues re-evaluating the appropriate size of laryngeal mask airway (LMA) in males and females.[1] The authors found that larger sizes have a more effective seal, but came up into the mouth more often, which could interfere with tonsillectomy and could increase the risk of sore throat or lingual nerve damage. The value of this study would be greatly improved if the authors could provide additional information.

First, the data do not necessarily support these findings as no mention is made of the volume of air used to inflate the cuff. This makes inter-size comparisons difficult as the efficacy of the seal, fibreoptic position[2] and (probably) the extent to which the cuff protrudes into the mouth are related to cuff volume. Second, if the cuff is seen in the oral cavity, we agree that a smaller size should be used for tonsillectomy, but we do not agree that a smaller size should be used if prolonged surgery is expected. The authors' rationale for this latter recommendation is that the presence of the cuff in the oral cavity might increase the risk of oropharyngeal morbidity. We are unaware of any data supporting this hypothesis and are concerned that the process of multiple insertion could itself increase the risk of oropharyngeal morbidity. The authors may be able to clarify this matter if they could provide postoperative morbidity data from their study population, as the LMA was inserted into each patient on 2–3 occasions. Third, the authors assessed the presence/absence of gas leaks around the mask at airway pressures of 10 and 18 cm H_2O. Several tests have been described to assess leaks: each differs slightly in accuracy and inter-observer reliability.[3] It would be useful to know which test was used. Fourth, in the discussion, the authors indicate that the population studied was Oriental. It is a commonly held belief that smaller masks are easier to use in Oriental patients. Could the authors comment on the reason for failed placement in the three patients noted in Table 1? Were there any data on the time to successful placement between different mask sizes?

Finally, the authors imply that smaller LMA would commonly be required for tonsillectomy as the larger masks protrude into the oral cavity in 24–45% of patients. We consider this recommendation to be weak as the frequency with which the cuff protrudes into the mouth may be less with the flexible LMA (which has a smaller, more mobile tube that might be less likely to push the cuff into the oral cavity) and the presence of the cuff in the oral cavity may not interfere with surgical access to the tonsils. One of the authors (J.B.) has experience of 53 consecutive adult tonsillectomies with the flexible LMA (males size 5; females size 4) without any problems relating to surgical access.

J. Brimacombe
Department of Anaesthesia and Intensive Care
University of Queensland
Cairns Base Hospital, Australia
C. Keller
Department of Anaesthesia and Intensive Care
University of Innsbruck, Austria
J Sartain
Department of Anaesthesia and Intensive Care
Cairns Base Hospital, Australia

1 Asai T, Murao K, Yukawa H, Shingu K Re-evaluation of appropriate size of the laryngeal mask airway. *Br J Anaesth* 1999; **83**· 478–9
2 Keller C, Puehringer F, Brimacombe J. The influence of cuff volume on oropharyngeal leak pressure and fibreoptic position with the laryngeal mask airway. *Br J Anaesth* 1998; **81**: 186–7
3 Keller C, Brimacombe J, Keller K, Morris R. A comparison of four methods for assessing airway sealing pressure with the laryngeal mask airway in adult patients *Br J Anaesth* 1999, **82**· 286–7

Editor,—In our study,[1] we inflated the cuff initially with the recommended maximal volume of air (20 ml for size 3, 30 ml for size 4 and 40 ml for size 5) and gradually removed air from the cuff until gas leak around the mask was just prevented. With this method, cuff volume was about 25 ml when the size 4 in females and size 5 in males were used.[2]

Second, we did not claim that the smaller size should be used if prolonged surgery is expected. Instead, we stated that 'when the cuff of the laryngeal mask is seen [in the oral cavity], the decision to replace the mask with one size smaller *depends on several factors* For example, a small mask is *preferable* when . . surgery of a long duration is expected' (authors' italic).[2] The rationale for this claim was, as Dr Brimacombe and colleagues correctly state, 'the presence of the cuff in the oral cavity might increase the risk of oropharyngeal morbidity'. Of course, one should consider the increased risk of morbidity associated with multiple insertions. We did not formally study the incidence of postoperative sore throat and thus we cannot provide data regarding this factor.

Third, we assessed the presence or absence of air leak by hearing an audible noise around the mask. Fourth, the reason for failed ventilation through the laryngeal mask was the same in the three patients in Table 1—the mask came out of the mouth during inflation of the cuff. We did not measure the time taken for insertion of the mask.

Finally, the flexible and standard laryngeal masks have different tube structures, but they have masks of the same specifications. Therefore, theoretically, there should be no differences between the two types of device in the incidence of the mask being seen in the oral cavity. Dr Brimacombe's information of unproblematic use of the flexible laryngeal mask in 53 patients is useful, but it may have been that all of his patients were reasonably tall (patient height was not given in his report).

T. Asai
K. Shingu
Kansai Medical University
Moriguchi City, Osaka, Japan

1 Asai T, Murao K, Yukawa H, Shingu K. Re-evaluation of appropriate size of the laryngeal mask airway. *Br J Anaesth* 1999, **83**: 186–7

2 Asai T, Howell TK, Koga K, Morris S. Appropriate size and inflation of the laryngeal mask airway. *Br J Anaesth* 1998; **80**. 470–4

Local anaesthetic infiltration and natural killer cell cytotoxicity

Editor,—The study by Greisen and colleagues demonstrated that infiltration of local anaesthetic abolished the natural killer cell response to painful stimulation of abdominal wall skin.[1] This is an observation that cannot be refuted, but I must express serious concern that, on the basis of their results, they question the beneficial effect of local anaesthetic infiltration of surgical fields, and suggest that it may impair the response against certain microbial infections and dissemination of tumour cells The battle to improve the quality of surgical pain relief is difficult enough without such unqualified statements. I would make two specific points.

First, the experimental model used was one of acute pain 'without tissue injury'. I know of no surgical wound that is not associated with tissue injury and therefore would question the validity of the conclusions. I appreciate that a similar study *with* tissue injury would be unlikely to attract many volunteers, but that does not make their model clinically relevant.

Second, local anaesthetic infiltration has been used for surgical procedures for more than 100 yr, but there is no evidence that I am aware of that it predisposes to bacterial infection or dissemination of tumour cells. Can Greisen and colleagues provide any, and, if so, does that mean that they would have every minor surgical procedure performed under general anaesthesia instead? Perhaps they would revert to using no anaesthesia or analgesia at all!

Observation is easy. Considering the relevance of the observation is altogether more difficult.

J. A. W. Wildsmith
University Department of Anaesthesia
Dundee, UK

1 Greisen J, Hokland M, Grøfte T, Hansen PO, Jensen TS, Vilstrup H, Tønnesen E. Acute pain induces an instant increase in natural killer cell cytotoxicity in humans and this response is abolished by local anaesthesia. *Br J Anaesth* 1999; **83**: 235–40

Editor,—We thank Dr Wildsmith for his interest in our article. We never attempted to discredit the use of local anaesthetic infiltration for intra- and postoperative pain relief. Of course our data do not allow for this. Our purpose was to examine the natural killer (NK) cell response to acute pain per se and to discover if local anaesthesia could modify the response. Thus we were investigating the pathophysiology of pain and not that of surgery.

NK cells probably play a role as a first line of defence against certain tumour cells and virus infected cells,[1 2] and an increase in NK cell cytotoxicity (in the experimental situation against a specific tumour cell line) is taken to reflect an increase in the ability to damage deleterious cells. We noted that local anaesthesia blocked the NK cell response in addition to pain. Therefore, we raised the question if infiltration with local anaesthesia has a beneficial effect The question has to be taken as one for generating hypotheses and not as a conclusion.

The fact that local anaesthesia has been used for many years is not in itself proof of its safety. To our knowledge, there are no studies in humans on the importance of local anaesthetics on tumour dissemination or susceptibility to viral infections.

J Greisen
Department of Medicine V
E. Tønnesen
Department of Anaesthesiology
Aarhus University Hospital
Aarhus, Denmark

1 Whiteside TL, Herberman RB. Role of human natural killer cells in health and disease. *Clin Diagn Lab Immunol* 1994; **1**: 125–33

2 Biron CA Natural killer cell regulation during viral infection. *Biochem Soc Trans* 1997; **25**: 687–90

Double-lumen tube placement: protecting the good lung

Editor,—I congratulate Cheong and Koh[1] for their study that not only questioned accepted practice for double-lumen tube placement but also succeeded in showing that there is, after all, a better way.

They used the fibreoptic bronchoscope in the tracheal lumen of a left-sided double-lumen tube to observe, as it was happening, passage of the tube into the left main bronchus and inflation of its bronchial cuff. The twin advantages of speed and certainty of double-lumen tube placement make this a rational approach, especially in the presence of pneumothorax or where there is a need to protect a good lung from contamination from a diseased lung.[1] In the latter situation, however, the advantages may be lost if fibreoptic vision is impaired by the presence in the trachea of purulent secretions or blood.

In such cases, I have taught a tube placement procedure that has involved 'blind' initial insertion of a left-sided Robertshaw tube as the preferred double-lumen tube. I still believe that the relatively rigid anatomical shape of the Robertshaw reduces the likelihood of its entering the incorrect main bronchus during placement and, more importantly, of its becoming displaced in the course of surgery.

I was therefore keen to assess the merit of continuing with my old procedure but with the addition of the fibreoptic bronchoscope placed in the tracheal lumen of the left-sided Robertshaw tube during otherwise 'blind' placement. Unfortunately, I find that although the technique works very well for plastic double-lumen tubes such as the Mallinckrodt and Sheridan, the twin advantages are much less impressive with the Robertshaw tube. The distance between the bronchial and tracheal orifices of the Robertshaw tube is large in comparison with the plastic tubes, and its anatomical shape as it lies within the trachea serves as an obstruction to both the view and easy and safe advancement of the bronchoscope. Thus the carina and right main bronchial orifice may only be seen after the bronchial component has entered the left main bronchus. The fibreoptic bronchoscope is then useful for confirming that the transverse 'gutter' that identifies the proximal rim of the inflated bronchial cuff of the Robertshaw lies in the left main bronchus at or just beyond the carina.

I also teach that where it is anticipated that secretions or blood may impede fibreoptic vision, a right-sided Robertshaw should be available in case the left-sided tube persists in entering the right main bronchus.

Thus where protecting a good lung is paramount, my preferred technique continues to involve the Robertshaw double-lumen tube inserted 'blind', but I do intend to modify my regular practice to include seeing the inflated bronchial cuff before rather than after the routine of individual lung ventilation.

J. Pfitzner
Department of Anaesthesia
North Western Adelaide Health Service
Adelaide, South Australia

1 Cheong KF, Koh KF. Placement of left-sided double-lumen endobronchial tubes: comparison of clinical and fibreoptic-guided placement. *Br J Anaesth* 1999; **82**: 920–1

Editor,—We are grateful to Dr Pfitzner for his interest in our study. We agree that the use of our technique is hampered in cases where copious secretions or blood are present in the trachobronchial tree. In these cases, we merely withdraw the bronchoscope and proceed with blind placement as practised conventionally. Our experience with the Robertshaw double-lumen tube is limited and this type of endobronchial tube has not been available for some time in our institution. As such we would like to thank Dr Pfitzner for his helpful hints. The bronchoscope can only be an aid to placement of double-lumen tubes; it cannot replace conventional techniques in all cases.

K F Cheong
K. F. Koh
Department of Anaesthesia
National University Hospital
Singapore

Paediatric Resuscitation Guidelines

Editor,—Dr Zideman's article concerning paediatric resuscitation and the ILCOR guidelines,[1] including the current experimental and clinical evidence on which such recommendations are based, provided an excellent and concise review of the subject. However, a recent case has led me to question two statements made in support of the current guidelines. A 3.8-kg male baby, aged 5 days, underwent an exploratory laparotomy and removal of a left suprarenal tumour. Histology subsequently showed it to be a mesoblastic nephroma. Approximately 20 min after removal of the tumour, the baby suddenly became profoundly bradycardic and hypotensive (arterial saturation remaining normal) and then rapidly suffered an asystolic cardiac arrest. Multiple doses of epinephrine, volume replacement (colloid and blood), sodium bicarbonate and calcium chloride were given (according to currently accepted ILCOR and Resuscitation Council (UK) guidelines). After four doses of epinephrine, ventricular fibrillation developed which proved very resistant to treatment. Eventually, after the sixth attempt at defibrillation and following a fifth dose of epinephrine, a slow, broad complex rhythm associated with a spontaneous cardiac output returned. Atropine 20 $\mu g\ kg^{-1}$ produced rapid and sustained improvement in both heart rate and cardiac output. The baby made an excellent recovery and was subsequently discharged home with no signs of neurological impairment.

In his review, Dr Zideman stated that 'no children have survived to discharge who have received more than two doses of epinephrine'. The references used to support this statement studied the results after 'out of hospital' arrests where long 'down times' and relatively inadequate resuscitation could be confidently expected.[2 3] Dr Zideman also stated that in the ILCOR guidelines, atropine is 'not indicated during resuscitation as the adrenergic effects of epinephrine are considered to over-ride the parasympathetic (vagal) effects of atropine'. The exact cause of this infant's cardiac arrest is not known but was probably secondary to relative hypovolaemia with pre-existing impaired ventricular function. Before operation, this baby had been hypertensive requiring treatment with α and β blockers. Residual adrenergic block may have played a role in the aetiology of the cardiac arrest, in addition to the requirements for high doses of epinephrine. The effective response to atropine with such high circulating concentrations of catecholamines is also surprising. Perhaps residual β block was a contributory factor? The prompt recognition and treatment of this asystolic arrest was undoubtedly responsible for the eventual successful outcome. Clearly, such a short period between onset and effective treatment is highly unusual, especially in an 'out of hospital' situation and only adds strength to the emphasis placed on the early recognition and treatment of the critically ill child, as taught in resuscitation courses (e.g. Paediatric Advanced Life Support and Advanced Paediatric Life Support).

The guidelines recommended by the ILCOR and Resuscitation Council (UK) should be used but not rigidly adhered to without consideration of each individual case. Indeed, within the current guidelines, flexibility in therapy is 'allowed' when you 'consider and correct reversible causes'. Of course, this also requires flexibility of thought on the part of those leading the resuscitation. The potentially huge disparity in outcome between individual resuscitation cases depending on their aetiology and location, as illustrated by the case report here, must surely encourage a more cautionary approach to the use of such sweeping statements when associated with such widely read and important guidelines.

H Hack
Royal Manchester Childrens Hospital
Manchester, UK

1 Zideman DA. Resuscitation *Br J Anaesth* 1999; **83**: 157–68
2 Dieckman RA, Vardis R. High-dose epinephrine in paediatric out-of-hospital cardiopulmonary arrest. *Pediatrics* 1995; **95**: 901–13
3 Schindler MB, Bohn D, Cox P, *et al.* Outcome of out-of-hospital cardiac or respiratory arrest in children. *N Engl J Med* 1996; **335**: 1473–9

Editor,—I am delighted that Dr Hack has reported this unusual event where a 3.8-kg baby survived multiple doses of epinephrine and ventricular fibrillation without severe neurological damage.

At the beginning of my article[1] and in the ILCOR statement[2] it is explained that both are based on specific evidence where available, or supported on the basis of common sense or ease of teaching and skill retention. The paediatric ILCOR statement includes recommendations reached by consensus of an expert multinational panel. The specific published evidence was declared in the reference list. Dr Hack, by presenting this letter for publication, has therefore added to the data source and the results that he has reported would be considered, together with those reported via published paediatric Utstein template[3] reports, at the next review.

The paediatric resuscitation guidelines should not be considered as rigid protocols. I note that in his report, Dr Hack adhered to the recommended guidelines initially. In some events, especially when the cause is treatable and there is little or no monitored hypoxia, it is appropriate to continue resuscitation and to use any reasonable resource or treatment available. In this case, multiple administrations of epinephrine (dose not reported) were successful in restoring a spontaneous circulation. The use of atropine in the treatment of the resulting peri-arrest bradycardia was appropriate, despite the anomaly of the previous multiple doses of epinephrine. Finally, may I suggest that the success of this event was a result of sustained maintenance of tissue oxygenation. It cannot be emphasized sufficiently that sustained delivery of oxygen to this infant's tissues was critical to the successful outcome.

I would hope that the publication of this letter will encourage others to report their paediatric resuscitation events, either as individual case reports or using the Utstein template,[3] so that we can continue to improve the practice of paediatric life support.

D A Zideman
Department of Anaesthesia
Hammersmith Hospital
London, UK

1 Zideman, DA. Resuscitation. *Br J Anaesth* 1999; **83**: 157–68
2 Nadkarni V, Hazinski MF, Zideman DA, *et al.* Paediatric life support: an advisory statement by the Paediatric Life Support Working Group of the International Liaison Committee on Resuscitation. *Resuscitation* 1997; **34**: 115–27
3 Zaritsky A, Nadkarni V, Hazinski MF, *et al.* and the Paediatric Utstein Consensus Panel. Recommended guidelines for uniform reporting of paediatric advanced life support: the paediatric Utstein style. *Resuscitation* 1995; **30**: 95–116

Which is better in children: edrophonium or neostigmine?

Editor,—We read with interest the review article by Fisher[1] on neuromuscular blocking agents in paediatric anaesthesia. It was a concise summary of the use of these agents in paediatric practice today. The author's preference for edrophonium over neostigmine, however, did not seem to be a true reflection of what is known about antagonism of neuromuscular block in children

There have been few comparative studies in children of the speed of action of edrophonium and neostigmine. In comparable mg per kg doses, recovery from an intense atracurium-induced neuromuscular block in children is faster after neostigmine than edrophonium.[2] In adults, it has been shown that in the reversal of profound block produced by vecuronium or atracurium, neostigmine is more effective than edrophonium and its maximal effect is reached more quickly, even though edrophonium is faster in its initial onset.[3 4] Monitoring of the depth of neuromuscular block in infants and children is technically more difficult and not perhaps as widespread as in Dr Fisher's department. This suggests that the chance of profound neuromuscular block at the end of surgery is greater in paediatric anaesthetic practice. Neostigmine would therefore be a better choice than edrophonium.

In his article, Fisher stated that less neostigmine is needed in children than in adults, and quoted Fisher and colleagues.[5] Quoting the same article,[5] he then stated that the ED_{50} of neostigmine for antagonism was greater for children than for adults. It is possible that this is a typing error and that the author means to suggest that edrophonium has a higher ED_{50} in children than in adults.[6] For this reason, the author suggests the use of higher doses of edrophonium for antagonism in infants and children. These studies, however, were carried out under steady-state infusion of tubocurarine and not during the recovery phase from the newer non-depolarizing agents. Moreover, there was no significant difference in the dose of edrophonium required to antagonize tubocurarine-induced neuromuscular block in children and adults [6] In contrast, several studies have shown that neostigmine antagonizes residual non-depolarizing neuromuscular block more effectively in children than in adults.[7–9] Debaene, Meistelman and d'Hollander[7] showed that, when twitch height recovered to 10% of control after vecuronium, neostigmine 30 $\mu g\ kg^{-1}$ had a more rapid onset in children than in adults, and that a TOF of 0.7 was obtained in less than 10 min in all patients, including infants. The dose of neostigmine to effectively antagonize 90% block produced by rocuronium is indeed smaller in children (mean 7 $\mu g\ kg^{-1}$) than in adults (56 $\mu g\ kg^{-1}$).[8] The effects of 2 × ED_{95} of rocuronium could effectively be antagonized in infants with neostigmine 20 $\mu g\ kg^{-1}$.[9]

With mivacurium there may be an argument for the use of edrophonium as it slows the hydrolysis of mivacurium by plasma cholinesterase less than neostigmine. However, until this issue is resolved, we agree with the author's recommendation of not antagonizing profound mivacurium-induced block.

In summary, we feel that there are little convincing scientific data to prefer edrophonium to neostigmine in paediatric patients. Indeed, with the new shorter acting neuromuscular blocking agents, there may be some advantage to the use of neostigmine over edrophonium.

J J Driessen
E. N. Robertson
L. H. D J Booij
Department of Anaesthesiology
Academic Hospital Nijmegen
Nijmegen, The Netherlands

1 Fisher DM. Neuromuscular blocking agents in paediatric anaesthesia. *Br J Anaesth* 1999, **83**: 58–64
2 Gwinnutt CL, Walker RWM, Meakin G Antagonism of intense atracurium-induced neuromuscular block in children. *Br J Anaesth* 1991; **67**: 13–6
3 Caldwell JE, Robertson EN, Baird WLM Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium Comparison of neostigmine with edrophonium *Br J Anaesth* 1986, **58**: 1285–9
4 Caldwell JE, Robertson EN, Baird WLM. Antagonism of vecuronium and atracurium: comparison of neostigmine and edrophonium administered at 5% twitch height recovery *Br J Anaesth* 1987; **59**: 478–81
5 Fisher DM, Cronelly R, Miller RD, Sharma M The neuromuscular pharmacology of neostigmine in infants and children. *Anesthesiology* 1983;**59**: 220–5
6 Fisher DM, Cronelly R, Sharma M, Miller RD. Clinical pharmacology of edrophonium in infants and children. *Anesthesiology* 1984, **61**: 428–33
7 Debaene B, Meistelman C, d'Hollander A. Recovery from vecuronium neuromuscular blockade following neostigmine administration in infants, children and adults during halothane anaesthesia *Anesthesiology* 1989, **71**: 840–4
8 Abdulatif M, Mowafi H, Al-Ghamdi A, El-Sanabary M. Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults. *Br J Anaesth* 1996, **77**: 710–15
9 Leuwer M, Motsch J, Schledt U, *et al.* Dose–response, time course of

action and recovery of ORG 9426 (rocuronium) in infants during halothane anaesthesia. *Br J Anaesth* 1994; **73**· 716P

Editor,—Driessen, Robertson and Booij challenge my preference for edrophonium over neostigmine. The first issue that they explore is profound block. My review acknowledges that neostigmine is preferred in that setting. Even if they are correct that 'monitoring of infants is technically more difficult', I hope that neuromuscular block is monitored routinely in infants. I also expect that clinicians are able to distinguish between profound twitch depression at the time of antagonism[1] (no response to train-of-four stimulation) from the more typical level of recovery (presence of more than one twitch in response to train-of-four stimulation). Under these usual conditions, is there evidence to refute my claim that edrophonium works faster?

Driessen, Robertson and Booij detected a typographical error that I wish to correct. The ED_{50} for edrophonium (not for neostigmine) is larger in children (233 $\mu g\ kg^{-1}$) than in adults (128 $\mu g\ kg^{-1}$). Although the difference was not significant, the larger value and larger variability in children than in adults led to our recommendation 'that paediatric patients receive larger doses of edrophonium (e.g., 1.0 $mg\ kg^{-1}$)[2] than adults.

Driessen, Robertson and Booij then claimed that three studies demonstrated that 'neostigmine antagonizes residual non-depolarizing neuromuscular block more effectively in children than in adults'. Unfortunately, they mis-state the conclusions of those studies. Debaene, Meistelman and d'Holland[3] found no difference between infants, children and adults for recovery of twitch at any time or in the train-of-four response before 10 min. They attribute the improved late train-of-four recovery in children to 'the faster rate of spontaneous recovery from vecuronium', rather than an effect of the antagonist. The results of Abdulatif and colleagues[4] also can be explained by the more rapid spontaneous recovery in children than in adults (as evidenced by their control groups). Leuwer and colleagues' abstract[5] reported that neostigmine 20 $\mu g\ kg^{-1}$, given at 25% recovery, improved the time to train-of-four >0.7 in infants (no adults were studied) compared with a group given no antagonist; however, variability in recovery rate was quite large (SD exceeded the mean) and no other neostigmine doses were evaluated.

Driessen, Robertson and Booij concluded that 'there is little convincing scientific data to prefer edrophonium to neostigmine in paediatric patients' and suggest that 'with the new shorter acting neuromuscular blocking agents there may be some advantage to the use of neostigmine over edrophonium'. In contrast, studies in children[2 6] and adults[7 8] demonstrate that edrophonium antagonizes 90% block faster than neostigmine. Hence, whenever block is not intense and recovery time is important (as is increasingly true in clinical anaesthesia), I prefer edrophonium in children.

D. M. Fisher
Department of Anesthesia
University of California
San Francisco, CA, USA

1 Gwinnutt CL, Walker RW, Meakin G. Antagonism of intense atracurium-induced neuromuscular block in children. *Br J Anaesth* 1991; **67**. 13–16

2 Fisher DM, Cronnelly R, Sharma M, Miller RD. Clinical pharmacology of edrophonium in infants and children. *Anesthesiology* 1984; **61**: 428–33

3 Debaene B, Meistelman C, d'Hollander A. Recovery from vecuronium neuromuscular blockade following neostigmine administration in infants, children, and adults during halothane anesthesia. *Anesthesiology* 1989; **71**: 840–4

4 Abdulatif M, Mowafi H, al-Ghamdi A, el-Sanabary M. Dose–response relationships for neostigmine antagonism of rocuronium-induced neuromuscular block in children and adults. *Br J Anaesth* 1996; **77**: 710–15

5 Leuwer M, Motsch J, Schledt U, *et al.* Dose–response, time course of action and recovery of Org 9426 (rocuronium) in infants during halothane anaesthesia. *Br J Anaesth* 1994, **73**. 716P

6 Fisher DM, Cronnelly R, Miller RD, Sharma M Neuromuscular pharmacology of neostigmine in infants and children *Anesthesiology* 1983,**59**. 220–5

7 Cronnelly R, Morris RB, Miller RD Edrophonium. Duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 1982; **57**· 261–6

8 Miller RD, VanNyhuis LS, Eger EI II, et *al* Comparative times to peak effect and durations of action of neostigmine and pyridostigmine. *Anesthesiology* 1974; **41**: 27–33

Bacterial contamination of needles used for spinal and epidural anaesthesia

Editor,—We read with interest the article by Raedler and colleagues regarding contamination of needles used during central neural block.[1] It is cause for concern that almost 18% of the needles showed evidence of bacterial contamination, even though no patient developed infective complications. There are points we would like to make with regard to the aseptic technique which may explain the high incidence of bacterial colonization.

First, it is not clear if the 10% polyvidone–iodine (PI) used for skin preparation came from single or multiple-use containers. There is evidence to show that multiple-use PI bottles in normal use may become contaminated by bacteria and also that the solution is less effective than PI from previously unopened bottles.[2] Also, alcohol chlorhexidine is a commonly used alternative to PI for skin disinfection and has been shown to reduce the rate of central venous catheter colonization and catheter-related sepsis compared with PI.[3 4] There are no studies comparing the two solutions for skin disinfection before central neural block, but we would suggest that it should be used in preference to PI.

Second, the authors refer to the use of sterile gloves and drapes, but no mention is made as to whether face masks were worn. While we accept that the use of face masks has not been shown to decrease the incidence of postoperative surgical wound infection,[5] there is evidence to suggest that they decrease bacterial dispersion[6] and that their use can reduce the incidence of catheter-related infections during insertion.[7]

We suggest that the use of alcohol chlorhexidine instead of 10% PI and wearing of face masks for central neural block may reduce the incidence of bacterial contamination of spinal and epidural needles.

J Whiteside
J A W Wildsmith
University Department of Anaesthesia
Dundee, UK

1 Raedler C, Lass Florl C, Puhringer F, *et al* Bacterial contamination of needles used for spinal and epidural anaesthesia. *Br J Anaesth* 1999; **83**: 657–8

2 Birnbach D, Stein D, Murray O, Thys D, Sordillo E. Povidone iodine and skin disinfection before initiation of epidural anesthesia. *Anesthesiology* 1998, **88**· 668–72

3 Mimoz O, Pieroni L, Lawrence, C, et *al.* Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Crit Care Med* 1996, **24**: 1818–23

4 Legras A, Cattier B, Dequin P, Boulain T, Perrotin D. Prospective randomised trial for prevention of vascular catheter infection: Alcohol

chlorhexidine versus povidone–iodine. *Reanimation Urgences* 1997; **6**: 5–11

5 Tunevall T. Postoperative wound infections and surgical face masks: a controlled study. *World J Surg* 1991; **15**: 383–7

6 Philips J, Fergusson S, Armstrong P, Anderson F, Wildsmith J. Surgical face masks are effective in reducing bacterial contamination caused by dispersal from the upper airway. *Br J Anaesth* 1992; **69**: 407–8

7 Raad I, Hohn D, Gilbreath B, *et al.* Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol* 1994; **15**: 231–8

Editor,—Raedler and colleagues[1] described an incidence of 17.9% bacterial contamination of spinal and epidural needles after lumbar puncture of the subarachnoid or epidural space. The authors make the important point that despite using an aseptic technique, lumbar puncture may contaminate spinal and epidural needles. Their aseptic technique included skin disinfection with 10% polyvidone–iodine (Braunol 2000). Povidone–iodine is a complex of iodine, the bactericidal component, with polyvinylpyrrolidone (povidone) a synthetic polymer. The common commercial form in the UK is a 10% solution in water (Betadine).

In vitro studies showed that aqueous povidone–iodine (PI) preparations were superior to alcohol or chlorhexidine preparations when tested for activity against bacteria with increasing dilution.[2 3] However, addition of 80% ethanol to 0.5% chlorhexidine significantly increased its potency and onset of action compared with 10% PI.[4]

The advantages of using alcohol rather than aqueous based solutions are further demonstrated by *in vivo* studies. Sato, Sakuragi and Dan[5] excised skin specimens from 60 patients undergoing elective back operations after preparation with either aqueous 10% PI or 0.5% chlorhexidine in 80% ethanol, and cultured staphylococcal species in 32.4% *vs* 5.7%, respectively.

A further problem, raised by Birnbach and colleagues,[6] concerns the frequency of bacterial contamination of previously opened multiple-use bottles of aqueous 10% PI. Bacteria were found only in previously opened bottles of which 40% were contaminated. Hence the study recommends single-use containers.

PI in an alcoholic solution overcomes the disadvantages of aqueous solution. A comparison of the efficacy of 10% PI ethanol solution and 0.5% chlorhexidine ethanol solution[7] showed no significant difference in decreasing skin bacterial counts (bacterial reduction rate 95% *vs* 93.5%).

Complete eradication of indigenous bacteria is impossible using the currently available skin disinfecting methods. However, to reduce the risk of infectious complications of epidural anaesthesia, attention should focus on any means of prevention, including optimal skin disinfection. Raedler and colleagues do not state if their PI solution was aqueous based or came from previously opened multi-use bottles. They recommend further improvement of hygienic measures but do not include optimization of skin disinfection with an alcoholic solution of 10% PI or 0.5% chlorhexidine.

E Chojnowska
Frenchay Hospital
Bristol, UK

1 Raedler C, Lass-Florl C, Puhringer F, Kolbitsch Ch, Lingnau W, Benzer A. Bacterial contamination of needles used for spinal and epidural anaesthesia. *Br J Anaesth* 1999; **83**: 657–8

2 Michel D, Zach GA. Antiseptic efficacy of disinfecting solutions in suspension test in vitro against methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli in pressure sore wounds after spinal cord injury. *Dermatology* 1997; **195** (Suppl. 2). 36–41

3 McLure AR, Gordon J. In-vitro evaluation of povidone–iodine and chlorhexidine against methicillin-resistant Staphylococcus. *J Hosp Infect* 1992; **21**: 291–9

4 Sakuragi T, Yanagisawa K, Dan K. Bactericidal activity of skin disinfectants on methicillin-resistant Staphylococcus aureus. *Anesth Analg* 1995; **81**. 555–8

5 Sato S, Sakuragi T, Dan K. Human skin flora as a potential source of epidural abscess. *Anesthesiology* 1996; **85**: 1276–82

6 Birnbach DJ, Stein DJ, Murray O, Thys DM, Sordillo EM Povidone iodine and skin disinfection before initiation of epidural anesthesia. *Anesthesiology* 1998; **88**: 668–72

7 Arata T, Kamitani M, Miyai T, Ito M. Antiseptic effects at injection sites. *Dermatology* 1997; **195** (Suppl. 2). 107–10

Editor,—Our aim was to study our practice of administering spinal or epidural anaesthesia; our technique was guided by generally recognized rules. We used aqueous povidone–iodine (PI). Face masks were not used in all cases, but there was no correlation between the use of face masks and needle contamination in our study. We are aware of the study published by Birnbach and colleagues[1] who found 40% of multiple-use PI bottles to be microbiologically contaminated compared with 5% contamination rate in bottles used for the first time. Hence they suggest single-use bottles for skin disinfection. Small bottles of PI for single use are not available in our country Moreover, Birnbach and colleagues stated that none of the organisms isolated from the sponge sticks used for skin disinfection was present in the PI solution, except in one case. Thus contamination is more a problem of normal skin colonization than of contaminated disinfection solutions We found our multiple-use PI solutions to be free of bacterial growth. However, Birnbach and colleagues speculated that reduced antimicrobial activity of PI solutions from multiple-use bottles might have been the reason for their findings.

Another point raised was that alcoholic PI might be superior to aqueous solutions. We found our antimicrobial solutions eradicated bacteria after weeks of use. But our results demonstrated that standards and guidelines must be subject to continuous evaluation. Despite using an aseptic technique, lumbar puncture may contaminate spinal or epidural needles. In line with Birnbach and co-workers, we conclude that indigenous bacterial skin flora is most likely the source of this contamination. Alcoholic solutions may be more effective in this respect.

C. Raedler
Department of Anaesthesia
University Hospital Innsbruck
Innsbruck, Austria

1 Birnbach DJ, Stein DJ, Murray O, Thys DM, Sordillo EM Povidone iodine and skin disinfection before initiation of epidural anesthesia. *Anesthesiology* 1998; **88**: 668–72

British Journal of Anaesthesia **84** (2). 296–7 (2000)

Book Reviews

Pain the Science of Suffering. P.D. Wall. Published by Weidenfeld and Nicolson, London. Pp. 178; indexed; illustrated. Price £14.99.

Patrick Wall is an intellectual colossus in the pain world, and he has written a lovely book. There can be something magical when a wise person looks back over the field which they have studied for many years. This book has that magic, clear writing coupled with insight.

The science is leavened by stories, vignettes about people and their pain. These Professor Wall uses to illustrate the complexity of pain, and to show how daft it is to expect simple solutions when the problem is anything but simple. The science is physiology with some pharmacology, and is written for an intelligent lay reader. It is followed by chapters on pain with obvious cause, and pains without such obvious cause. These are clearly and fairly written. The misery of fibromylagia, for instance, is not dismissed just because we do not understand the cause.

Chapters about treatments allow Professor Wall to expand his important theme, important for both patients and doctors, that miraculous cures are unlikely to emerge in chronic pain from interventions which cause permanent damage to the nervous system. The inevitable 're-wiring' may result in worse pain, albeit after a pain-free period. Our ignorance about the mechanisms of treatments which work is well covered, with an open intellectual curiosity. The sections on complementary medicine are entertaining and fair. The concept of hypnosis underlying acupuncture made me think. *Caveat emptor* would be an appropriate conclusion.

Towards the end of the book comes the suggestion that the brain representation of pain in common with some other sensations may be as the likely motor response. The distinction drawn is between pain as a signal of a painful stimulus or pain as a signal of 'the stage reached in a sequence of possible actions'. Here Professor Wall elegantly mops up placebo effects. He argues that if the sensation of pain is associated with a series of potential actions, remove painful stimulus, change posture, seek safety, apply therapy, and my experience is that a particular action is followed by relief, then I achieve relief if I think that action has occurred.

This book is recommended. At one level it should help people with chronic pain to understand that they have not necessarily gone crazy, and that there may be no simple remedy. For those of us who treat pain, it is a necessary and enjoyable read.

H. McQuay

Video Seminars of Transoesophageal Echocardiography. T. Rafferty. Published by Echocardiography.Org, Silverspring, Maryland, USA. Pp. 126 + 8 videotapes; indexed; illustrated. Price US$542.00.

As intraoperative transoesophageal echocardiography (TOE) gains pace in the UK, we are fortunate in being able to benefit from the increasing amount of teaching material emerging from the USA. The author if these videotape seminars, Dr Terence D. Rafferty, is professor and chief of cardiac anaesthesia at Yale University School of Medicine. He has many previous publications on the subject of TOE, most notably his excellent textbook, *Basics of Transesophageal Echocardiography*.

The series of seminars comprises a textbook and eight videotapes between 26 and 111 min long. The seminars cover transverse, vertical and oblique plane imaging, the mitral valve and mitral valve repair, critical care, total hip replacement and finally a 34 question transverse plane self-assessment test.

The accompanying textbook is far superior to the videotapes both in content and presentation. It is eloquently written, comprehensive and well referenced, with a clarity that is obviously Dr Rafferty's natural style. It would be useful if the book gave guidance on how to use the seminar material—ideally, the book should be read first and then the videotape viewed as illustration of the text. If the videotapes are viewed first, the tape commentary is frustratingly low on information about the interpretation and significance of the abnormalities shown, and the images pose more questions than they answer.

Dr Rafferty has, I think, been let down by the audio-visual company which produced the series, for they fail to make good use of the visual opportunities provided by the medium of videotape. For example, there are a large number of still images and long passages of text displayed on screen, and failure to marry commentary with the relevant video sequences. Many of the tapes show Dr Rafferty narrating long explanatory sections in which the information is presented as if in a lecture, with rather monotonous descriptions of the video images about to be shown. The ensuing TOE examination sequences, some excessively long, are then displayed in silence, without any simultaneous commentary. This problem makes the presentation somewhat tedious and I must confess to having nodded off frequently during the explanatory segments, only to have to rewind the tape when the images were shown to see whether any comment was made on an aspect of the image which I had noticed. Not all of the tapes suffer from this particular problem, and the non-uniform nature of the presentational styles makes the series appear somewhat disjointed. It is unfortunate that the tapes do not conform even to the same image orientation on the screen; changing the orientation without comment, especially after careful description of the image orientation used in the introductory tapes, is surely confusing to the novice. Similarly, commentary to describe the changing planes of interrogation (which are not annotated on screen) during an examination sequence would make a big difference to any learner.

Having personally attempted to make videotapes suitable for teaching in the past, I appreciate that it can be difficult to attain excellent examples of any particular view, even when collecting the images prospectively. However, having paid US$542 for this series of seminars, one might be forgiven for feeling a little cheated on that score. While there is something to be said for presenting sequences from the real world where nothing is perfect, the disadvantage is that the trainee transoesophageal echocardiographer is not given an idea of the 'ideal image' for which to strive while learning the technique. In addition, the image quality is frequently not good, particularly in sequences showing colour Doppler It is possible that the images have suffered somewhat as a result of having been copied and translated from their presumed native NTSC format into PAL for the European market.

With regard to the individual topics covered, the three tapes which deal with the practical acquisition of an echo image are clear and simply presented. The introduction to each of these three tapes, however, in which the relevant theory is covered, is dreary and is probably unnecessary if it is envisaged that the user will read the accompanying text first.

The remaining topics are fairly selective; the material covering the mitral valve only covers disorders of excessive leaflet motion for example, but the section for suggested further seminar topics which is contained in the registration card for the seminars suggests

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

that the series will become more comprehensive with time (the registration card also entitles the purchaser to discounts on future video seminars).

The tapes covering specific aspects of TOE are useful in providing reference images of different pathologies (and those covering critical care and mitral valve repair were particularly good in this regard), but they need better commentary. For example, I found it frustrating to be shown repeated images of persistent mitral regurgitation after mitral valve repair procedures with no comment on the assessment of the severity, significance and subsequent management of the residual regurgitation in that specific patient As such the tapes alone would not equip a trainee echocardiographer with the knowledge to interpret the clinical implications of what he sees so that he could give useful information to the surgeon. The textbook, however, has excellent discussion on the topic, with good explanations of nomenclature and intraoperative features, such as the haemodynamic effects of anaesthesia and sternotomy, and their influence on the images obtained It is unfortunate that the interpretative and discursive content of the text has not been used in the video commentary, as it would increase the value of the tapes enormously.

The seminar covering total hip replacement includes some interesting and unusual video images in the form of three case presentations. The accompanying text is well written, but this is a strange choice of topic for inclusion with the initial group of seminars. Perhaps it would have been better to include a subject of interest to more doctors who practice intraoperative TOE, such as coverage on aortic valvular disease or ventricular function. The self-assessment test is useful and fun, but its educational value would be much enhanced by an explanation of the answers.

Who should buy this series? It is hard to know the intended audience. The stated aim of the seminars is to teach TOE skills for both awake and intraoperative use without the need for apprenticeship, in other words to facilitate 'distance learning'. It is also suggested that experienced practitioners may find that adoption of the 10-step horizontal plane examination sequence described may improve their efficiency. If the seminars are aimed at the novice echocardiographer, then the omission of each teaching material on Doppler techniques is a serious one, as all but the most eccentric practitioners must regard Doppler as an important part of the examination sequence. In addition, increasing access to multiplane imaging would make an integrated multiplane examination taught as a single sequence of far more use than separate horizontal, vertical and oblique plane examinations. If, however, the series is aimed at more experienced practitioners who have already mastered the art of image acquisition, most of the introductory material, contained in the first three tapes, is superfluous.

Is this series of seminars worth the cost? Although the accompanying textbook is well worth having, I think that the videos themselves are disappointing. Dr Rafferty is a respected and acknowledged teacher in the field of intraoperative TOE, and I think the videotapes do not do him justice. They would be an expensive addition to any departmental library, for my money I would rather buy a CD-ROM atlas which is more user-friendly and can provide easily accessible commentary on the video clips shown, at a fraction of the price.

S. Wright

Drugs in Anaesthetic and Intensive Care Practice. 8th Edn M.D. Vickers, M. Morgan, P.S.J. Spencer and M S. Read. Published by Butterworth Heinemann, Oxford Pp 526; indexed; illustrated. Price £55.00.

This well-known multi-author book is now in its eighth edition; I can well remember its first appearance in 1962. The book has clearly stood the test of time, and its repeated publication is a testimony to its popular appeal. Eight years have passed since the appearance of the last edition; it will be interesting to see how the eighth edition stands up to the challenges of the new millennium.

In this edition, an additional co-author has been recruited, and the title of the book has been altered slightly. After an introductory chapter devoted to general pharmacology, most of the remaining 19 chapters deal with specific groups of drugs and their uses; only about 150 pages are devoted to commonly used anaesthetic drugs.

The first chapter covers a wide range of subjects, and some of them are necessarily dealt with in a fairly superficial manner. The sections on receptors, drug action and pharmacokinetics were reasonably good; I was surprised that the chapter made no mention of context-sensitive half-times, and did not attempt to describe the different forms and functions of cytochrome P_{450}

Most of the remaining chapters have a common format. Each begins with an account of the pharmacology of a single group of drugs, followed by a series of identically arranged monographs which deal with individual drug entities. Clearly, the initial account is intended to be read or studied, while the monographs are intended primarily for reference. Unfortunately, differentiation between the two is not always clear, and in my view this approach inevitably leads to a considerable amount of repetition. For example, in the monograph concerned with cimetidine, it states: 'Stimulated acid secretion, whether by gastrin, acetylcholine, food, sham feeding, fundic distension or various other pharmacological agents is also inhibited, a breadth of effect which clearly illustrates the pivotal role of histamine at H2 receptors in controlling gastric acid secretion In contrast, cimetidine has no consistent effect upon the rate of gastric emptying, the pressure of the lower oesophageal sphincter or subsequent pancreatic secretion'. There is nothing wrong with these statements. However, just three pages later, in the monograph on ranitidine, exactly the same two sentences are repeated verbatim, with the sole exception of a change in drug name. The book contains numerous other examples of this irritating phenomenon

In many ways this is a great pity, as the book has many good points. Many of the chapters provide accurate and succinct overviews of drugs; I was particularly impressed by the accounts of analgesics, neuromuscular blocking agents, anti-arrhythmic drugs and antibiotics In addition, it also contains useful clinical advice on the practical aspects of drug administration, and the text (and the appendix) provides an intelligent and relatively painless guide to the new recommended nomenclature for drugs (with which we will all have to contend during the next decade)

The book contains more than 70 structural formulae; surprisingly, these did not include a single local anaesthetic, inhalation anaesthetic or neuromuscular blocking agent. Some of the formulae are incorrect; for example, sulphur atoms have been omitted from three of the formulae in Figure 8.1 In addition, the book contains several other errors. For example, it states that 'compared with other common anaesthetic agents, halothane is relatively insoluble in blood', and that 'pirenzepine has some selectivity for M_3 receptors in the stomach' In the chapter on anticoagulants, they use the acronym APTT to refer to activated prothrombin time; it is unclear if they really mean activated partial thromboplastin time

Despite these criticisms, this book contains a lot of useful material and will be a valuable source of reference on drug information and nomenclature In my view, it is not a book designed to be read from cover to cover

T. N. Calvey

British Journal of Anaesthesia 84 (2): 298–300 (2000)

BJA

Acknowledgement of Assessors

The Editorial team are grateful to the following people who, in addition to the Editorial Board, helped in the assessment process in 1999:

A P Adams
S W A Adejumo
P J Adnet
A R Aitkenhead
R Aldridge
J I Alexander
E Allsop
R P Alston
J Amoore
J Andrade
C J H Andrews
P J D Andrews
A Angel
B Appadu
I Armstrong
F Arnstein
J E Arrowsmith
D S Arthur
T Asai
R A Atcheson
T Aziz

J L Bams
J Bannister
I Barker
P Barker
S V Baudouin
T Beattie
P C W Beatty
N M Bedforth
G Bell
M C Bellamy
N R Bennett
J L Benumof
J C Berridge
L Beydon
R J Beynon
R J S Birks
M Bock
M Bodelsson
A R Bodenham
M E Bone
B Bonke
P D Booker
J G Bovill
A Bowhay
G M R Bowler
J C Brearley
J F Brichant
S Bricker
J Brimacombe
Z L S Brookes
K Budd
D J Buggy
A G L Burm

G Calo
T N Calvey
D Cameron
I T Campbell
J Canet
F Carli
J N Cashman
J Cawley
W A Chambers
P Charters
H Chen
V A Clark
A T Cohen
A G H Cole
S Coley
B J Collett
P Collins
M O Columb
L A Colvin
I D Conacher
G M Cooper
D Counsell
C Court-Brown
D M Coventry
M Cross
R Cruickshank
A J Cunningham

A Dahan
J Dalton
M Davies
N Davies
M de Kock
C D Deakin
N M Dearden
D R Derbyshire
J P Desborough
M J Desmond
J C Devlin
A Dickenson
J Dinsmore
M B Dobson
C Dodds
S Dolin
J Donnelly
K L Dorrington
D J R Duthie

D L Edbrooke
N D Edwards
C Eintrei
D A Eisner
R H Elliot
C D Elton
J Evans

J Faccenda
L T Fahy
J Fairfield
P Farling
P Farquhar-Smith
W J Fawcett
J P H Fee
D Fell
R O Feneck
J Filshie
D M Fisher
R Fletcher
A Florence
C Flucker
P Flynn
P Foex
I D Forsythe
J E Fox
M Fox
J Freeman

H F Galley
D Galloway
C Garrard
L Gaspar
J S Gibson
R Glavin
R D Gleed
J B Glen
C Glynn
J C Goldstone
C M H Gomez
C S Goodchild
N W Goodman
J W W Gothard
G Gowland
I S Grant
W M Gray
R Greenbaum
J M C Greiff
R Griffiths
A B J Groeneveld
R M Grounds
B D Grubb

C Hahn
A Hainsworth
A P Hall
L W Hall
M H Hanna
C D Hanning
J G Hardman
M Harmer
N J N Harper
S J Harper
W M Harper
K P G Harris
S M Harrison
C R M Hay
B Hayes
M Heath
H C Hemmings
D J Henderson
J Henderson
C Heneghan
J Hester
D Heuser
S A Hill
D R Hillman
C J Hinds
K Hirota
R Hirst
G Hobbs
A Holdcroft
S J Howell
M J Hudspith
R Hughes
C J Hull
J E Hunsley
G L Hutchison

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

P Hutton

D E Iles

M F M James
R H James
U Janssens
J Jenkins
J R Johnston
D Jolliffe
G W Jones
J A Jones
J G Jones
R M Jones
D M Justins

U Kaisers
R Kato
G M A Keenan
H Kehlet
K Kelly
G N C Kenny
I G Kestin
D Kettler
J Kinsella
J Kirby
J Klein
S Knight
K Kong
K Korttila

J A Lack
O Langeron
J A Langton
I P Latto
A S Laurence
G G Lavery
P G Lawler
G Lees
M Leuwer
I D Levack
G Lewis
S P K Linter
S Lloyd
A R Lloyd-Thomas
A B Loach
G G Lockwood
M R Logan
P A Lonnqvist
A Lowy
C A Ludlam
A Lumb
J Lunec
G Lyons

T MacKay
W A Macrae
A P Madden
R P Mahajan
M Makris
S V Mallett
W W Mapleson
N Maran
R Marjot
I Marshall
R J Marshall
J Marty
R A Mason
L E Mather
B Matta
S Maxwell
W T McBride
W McCaughey
J H McClure
E McGrady
E G McKeating
S J McKenzie
D W McKeown
I McLellan
T J McMurray
H J McQuay
G H Meakin
J S Mecklenburgh
B M Meiklejohn
C Meistelman
D K Menon
H Metzler
R S Miles
K Millar
D C Miller
K Mills
R K Mirakhur
S Moise
E Moore
M Morgan
M D L Morgan
L M M Morrison
C P J Morton
N S Morton
E Moss
S M Mostafa
T C Muir
C Muller
R Munglani
P G Murphy
J Murray
P Musto
M G Mythen

K Nagendran
M Naguib
J Nally
D E F Newton
D A Nightingale
J Nightingale
A Nimmo
S Nimmo
J P Nolan
J Norman
R I Norman
W G Notcutt

H A O'Beirne
T O Carroll
E O'Sullivan
P Ake Oberg
A J Ogilvy
T E Oh
C H Orchard

G R Park
C J R Parker
J F Payen
S H Pennefather
J E Peacock
A C Pearce
J Peters
A Petros
B Phillips
I R Piper
B J Pleuvry
B J Pollard
C J D Pomfrett
J C Ponte
H Powell
C Prys-Roberts

P G Rabey
D Ray
D C Ray
A Reber
F Reynolds
A Rice
J Richardson
B Riou
J L Robotham
M Robson
D A Rocke
G Rolly
P Ross
D Rowney
D Royston
G B Russell
G N Russell
I F Russell
W Russell

P J Sadler
P Salmon
M S Sammut
R Sarginson
D A Saunderaq
M Scheinin
W Schlack
D H T Scott
R P F Scott
D Semple
J C Sewell
P Sharpe
R M Sharpe
N E Sharrock
E S Shearer
M P Shelly
K M Sherry
D Simpson
K H Simpson
P J Simpson
C Sirtl
D Smart
D C Smith
G L Smith
J E Smith
S L Snowdon
N Soni
J Sonksen
H Sonntag
M J Souter
D R Spahn
A A Spence
H J Spens
J S Sprigge
J A Stamford
R Stevenson
J Stocks
K Stuart-Smith
N Sutcliffe
D Swann
R A Swann

P M Taylor
H Teff
G Thind
D Thomas
T Thomas
J P Thompson
C Thornton
H Thurston
B Tiplady
A Tobin
A W Trafford
M R Tramer
T Trotter
G T Tucker

A Urwyler

R S Vaughan
C Verghese
L Versichelen
J Viby-Mogensen
A Vickers
A Vohra

R M Wahba
H G Wakeling
S W Walker
P G M Wallace
W M F Wallace
F J M Walters
J Wandless
J Y Y Wang
C A J Wardrop
A E Waterman
J Watkins
D Watson
W E Watson
J W H Watt
D Weatherill
D Weir
E Welchew
P Welsby
R Wenstone
C Werner
G A Weston
R J Wheatley
D C White
C Whitehead
R G Wilkes
G B Willars
S M Willatts
I G Wilson
M E Wilson
W Winlow
A R Wolf
J K Wood
P M C Wright
S Wright

P Yate
S M Yentis
A Yli-Hankala
C Young
Y Young

D A Zideman

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987, **59**. 14–23

Chapter in a book:

2. Hull CJ Opioid infusions for the management of postoperative pain In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985, 155–79

Monographs:

3. Moore, DC *Regional Block*, 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly

numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131–7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

The *British Journal of Anaesthesia* has implemented a change in reference style. We retain the Vancouver style, but the journal name is now abbreviated, only the change in the last page number is given and no full stop ends the reference (i.e. *Br J Anaesth* 1998; **81**: 232–9)

Reprints

We can now offer a reprints service for this journal

- Special journal cover
- Production quality equal to that of the original publication
- Timely shipping - including for international orders
- Simple ordering system
- Special pricing
- Available in minimum quantities of 100
- In compliance with copyright requirements

Contact:
Julie Gribben (please use the full journal name)
tel: +44 (0) 1865 267827;
fax: +44 (0) 1865 267782
e-mail: gribbenj@oup.co.uk
rpadjg898

OXFORD
UNIVERSITY PRESS

BJA
International Journal of Anaesthesia
Volume 84 Number 3 March 2000

EDITORIALS

301 I: Postoperative residual curarization and evidence-based anaesthesia
J. Viby-Mogensen

304 II: Neuropsychometric deficit after cardiac surgery: a new approach for a new millennium
M. Nevin

308 III: Placement of double lumen tubes—time to shed light on an old problem
S. H. Pennefather and G. N. Russell

CLINICAL INVESTIGATIONS

311 Effect of chronic intercurrent medication with β-adrenoceptor blockade or calcium channel entry blockade on postoperative silent myocardial ischaemia
J. W. Sear, P. Foex and S. J. Howell

316 Effect of midazolam on transfer function between beat-to-beat arterial pressure and inter-beat interval length
H. Schächinger, B. U. Müller, W. Strobel, J. Drewe and R. Ritz

323 Biphasic changes in autonomic nervous activity during pregnancy
C.-D. Kuo, G.-Y. Chen, M.-J. Yang, H.-M. Lo and Y.-S. Tsai

330 Transoesophageal echocardiographic assessment of haemodynamic changes during laparoscopic herniorrhaphy in small children
S. G. Sakka, E. Huettemann, G. Petrat, A. Meier-Hellmann, F. Schier and K. Reinhart

335 Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone
W. Funk, W. Jakob, T. Riedl and K. Taeger

341 S(+)-Ketamine for caudal block in paediatric anaesthesia
P. Marhofer, C. G. Krenn, W. Plöchl, T. Wallner, C. Glaser, H. Koinig, E. Fleischmann, A. Höchtl and M. Semsroth

346 Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration
B. V. S. Murthy, K. S. Pandya, P. D. Booker, A. Murray, W. Lintz and R. Terlinden

350 Comparison of compound A concentrations with sevoflurane anaesthesia using a closed system with a PhysioFlex anaesthesia machine vs a low-flow system with a conventional anaesthesia machine
H. Bito, A. Suzuki, Y. Sanjo, T. Katoh and S. Sato

354 Effects of the sitting position on the distribution of blood volume in patients undergoing neurosurgical procedures
W. Buhre, A. Weyland, K. Buhre, S. Kazmaier, K. Mursch, M. Schmidt, M. Sydow and H. Sonntag

358 Effects of fenoterol and ipratropium on respiratory resistance of asthmatics after tracheal intubation
R. S. C. Wu, K. C. Wu, T. K. M. Wong, Y. H. Tsai, R. K. S. Cheng, M. J. Bishop and P. P. C. Tan

363 Effect of cricoid pressure on insertion of and ventilation through the cuffed oropharyngeal airway
R. M. Dravid, P. Reed, M. Stoneham and M. T. Popat

367 Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials
E. Ernst and M. H. Pittler

LABORATORY INVESTIGATION

372 Effects of halothane on respiratory mechanics and lung histopathology in normal rats
G. S. Reta, J. A. Riva, H. Piriz, A. S. Medeiros, P. R. M. Rocco and W. A. Zin

REVIEW ARTICLE

378 Central nervous system complications of cardiac surgery
J. E. Arrowsmith, H. P. Grocott, J. G. Reves and M. F. Newman

SHORT COMMUNICATIONS

394 Residual curarization in the recovery room after vecuronium
C. Baillard, G. Gehan, J. Reboul-Marty, P. Larmignat, C. M. Samama and M. Cupa

396 Effect of intraoperative angiotensin-converting enzyme inhibition by quinaprilat on hypertension after coronary artery surgery
M. Müller, E. Schindler, M. Kwapisz, S. Klemm, H. Akintürk, M. Heidt and G. Hempelmann

399 Warm air sensation for assessment of block after spinal anaesthesia
J. Shah, B. T. Ayorinde, D. J. Rowbotham and D. J. Buggy

CASE REPORTS

401 Caudal clonidine for postoperative analgesia in adults
A. C. Van Elstraete, F. Pastureau, T. Lebrun and H. Mehdaoui

404 Preparation for regional anaesthesia induces changes in thrombelastography
H. Gorton, G. Lyons and P. Manraj

406 Rectally administered dimenhydrinate reduces postoperative vomiting in children after strabismus surgery
A. Schlager, G. Mitterschiffthaler and F. Pühringer

408 Postpartum headache after epidural blood patch: investigation and diagnosis
G. M. Stocks, D. J. A. Wooller, J. M. Young and R. Fernando

412 Patient-controlled analgesia in labour using remifentanil in two parturients with platelet abnormalities
J. A. Thurlow and P. Waterhouse

415 Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine
D. S. Ure, M. A. Gillies and K. S. James

417 CORRESPONDENCE

425 BOOK REVIEWS

428 ERRATUM

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists,
the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia,
and the Society for Intravenous Anesthesia

EDITORIALS

237 Cannabis: Time for Scientific Evaluation of this Ancient Remedy?
241 Small-Dose Neuraxial Block: Heading Toward the New Millennium

CARDIOVASCULAR ANESTHESIA
(Society of Cardiovascular Anesthesiologists)

243 Effective Stroke Volume Analysis
252 Regional Ventricular Elastances
262 Aprotinin: Significance of Antibodies at Exposure
267 Pulmonary Thromboendarterectomy and Treatment
274 Colloids and SONOCLOT-Measured Coagulation
280 Esmolol and/or Nicardipine and Tracheal Intubation
286 Postoperative Warming and Hemodynamics
292 Cardiovascular Surgery *Without* Cardiopulmonary Bypass in Patients with Heparin-Induced Thrombocytopenia Type II Using Anticoagulation with Recombinant Hirudin (Case Report)

PEDIATRIC ANESTHESIA
(Society for Pediatric Anesthesia)

299 Sedation for Pediatric Cardiac Catheterization
306 Sevoflurane, Halothane, and the Oculocardiac Reflex
311 Dimenhydrinate for Postoperative Vomiting
315 Comparison of the NAD 6000 and Servo 900C
322 A Massive Pulmonary Tumor Embolism After Surgical Manipulation and Biopsy of a Pelvic Mass (Case Report)

OBSTETRIC ANESTHESIA

324 Ephedrine, Hypotension, and Small-Dose Spinal Anesthesia
328 Patient-Controlled Epidural Analgesia During Labor
333 Human Amniotic Fluid and Thrombelastograph®
337 The Effect of Nitroglycerin on the Gravid Uterus

ECONOMICS AND HEALTH SYSTEMS RESEARCH

344 Reporting of Adverse Outcomes

CRITICAL CARE AND TRAUMA

351 Transesophageal Echocardiography and Preload Assessment in Critically Ill Patients
356 Perfluorocarbons Decrease Neutrophilic Infiltration After Acid Injury
362 *S*-Nitroso-N-Acetylpenicillamine Improves Vascular Hyporeactivity
369 Benzocaine-Induced Methemoglobinemia (Case Report)

NEUROSURGICAL ANESTHESIA

372 Changes in Cerebral Blood Volume with Position
377 Propofol-Ketamine and Cerebral Circulation

REGIONAL ANESTHESIA AND PAIN MANAGEMENT

383 Sufentanil and Brachial Plexus Block
388 Dopamine and Continuous Epidural Lidocaine
393 Mechanical Properties of Epidural Catheters
400 Spinal Antinociception by α_2 Agonists
408 Ketamine and Temporal Summation
415 Bupivacaine Enantiomers and Ropivacaine: Electrophysiology
421 Synergistic Interaction Between Morphine and Neostigmine
427 Oral Morphine vs IM Morphine for Postoperative Pain
431 Pharmacokinetics of Rectal Acetaminophen in Adults
437 Transient Neurologic Symptoms After Epidural Analgesia (Case Report)

GENERAL ARTICLES

440 Pharyngeal Pulse Oximetry
445 Nimodipine Premedication and Propofol Induction
450 Propofol/Sufentanil and Surgical Stress Response
456 Predictive Variables of Hypothermia
460 Comparison of Jet Ventilation Techniques
466 Inert Gas Exchange at Incremental Positive End-Expiratory Pressure
472 Ramosetron and Postoperative Nausea and Vomiting
476 Neuromuscular Blockers Inhibit the 5-HT_{3A} Receptor
482 NO and Anesthesia Machines
489 Cerebral Near-Infrared Spectrophotometry in Icteric Patients

TECHNICAL COMMUNICATION

494 Laryngeal Electromyography and Neuromuscular Block
498 LETTERS TO THE EDITOR
504 BOOK AND MULTIMEDIA REVIEWS

IARS PRECONVENTION ISSUE

SE
INFORMATIO
INSID

ISSN 0003-2999 Volume 90, Number 2, February 2000

Editorial Board

Editor-in-Chief

J. M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Senior Lecturer in Anaesthesia, *University of Leeds*
D. G. LAMBERT, Senior Lecturer in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. R. ELLIS, Professor of Anaesthesia, *University of Leeds*
W. FITCH, Professor of Anaesthesia, *University of Glasgow*
G. M. HALL, Professor of Anaesthesia, *University of London*
D. J. HATCH, Portex Professor of Anaesthesia, *University of London*
P. HUTTON, Vice-president, *Royal College of Anaesthetists*
R. D. MILLER, Professor of Anaesthesia, *University of California, San Francisco*
I. POWER, Associate Professor, *University of Sydney, Australia*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. SEAR, Clinical Reader in Anaesthesia, *University of Oxford*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Reader in Anaesthesia, *University of Plymouth*
L. STRUNIN, President, *Royal College of Anaesthetists*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Technical Editor

LINDA GOUGH

Please visit the Journals's World Wide Web site at http://bjanaes.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to BJA comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate

Institutions: UK and Europe £217, Rest of World US$346
Trainees: UK and Europe £105, Rest of World US$168
Single issue: UK and Europe £23, Rest of World US$36

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express, Diners, JCB); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; Email: jnl.info@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 80 onwards to* Oxford University Press. *For Vols 1–79* to Dawsons Back Issues, Cannon House, Folkestone, Kent. Tel: +44 (0)1303 203612; Fax +44 (0)1303 203617.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262.

© *The Board of Management and Trustees of the British Journal of Anaesthesia* 2000

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$346. British Journal of Anaesthesia is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

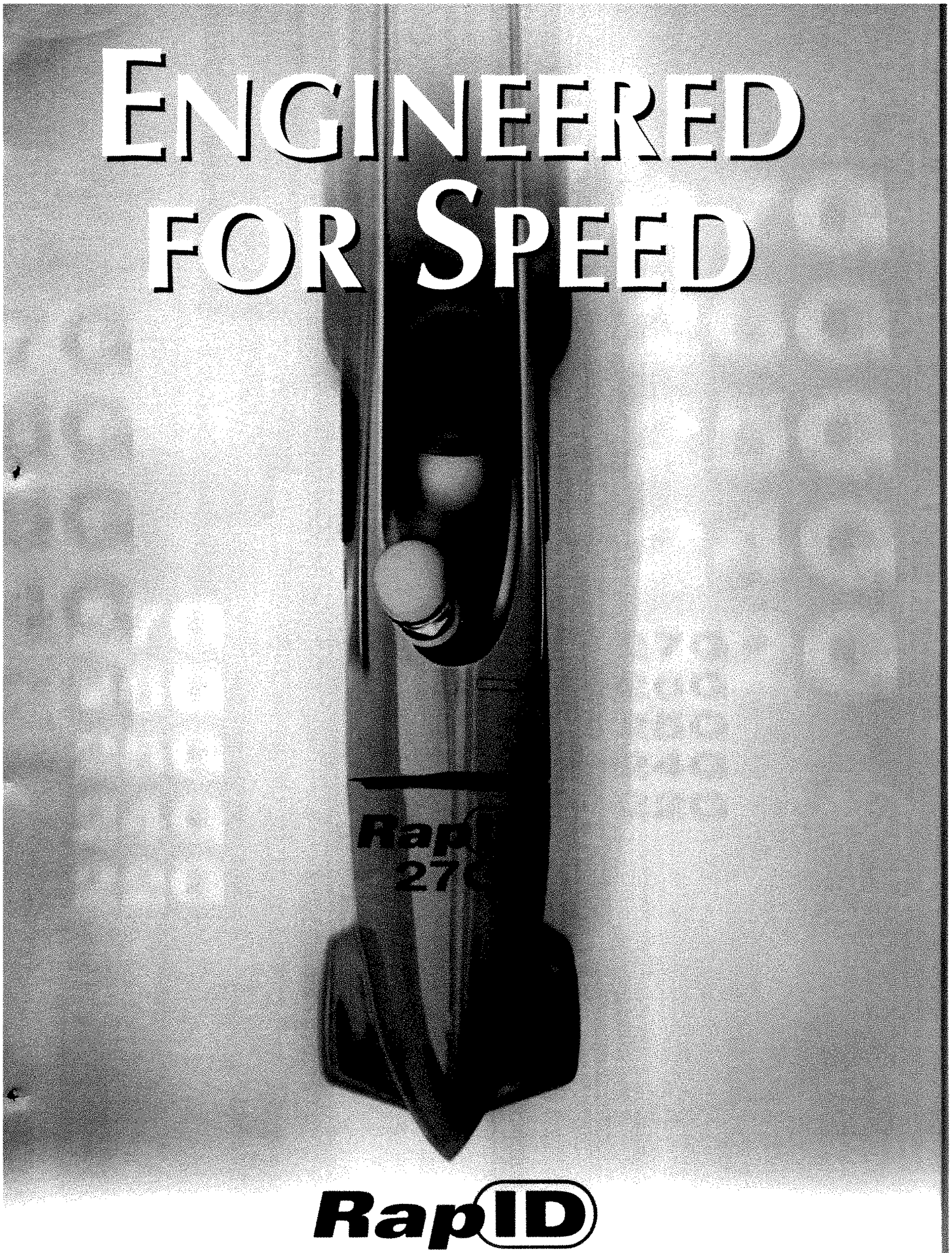
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000



SIMS is a world leading medical manufacturing group, with companies in Europe, North America, South Africa and the Pacific region, providing innovative products to critical care and community care professionals worldwide.

RapID

SUPERIOR FLASHBACK[1] SPINAL NEEDLES

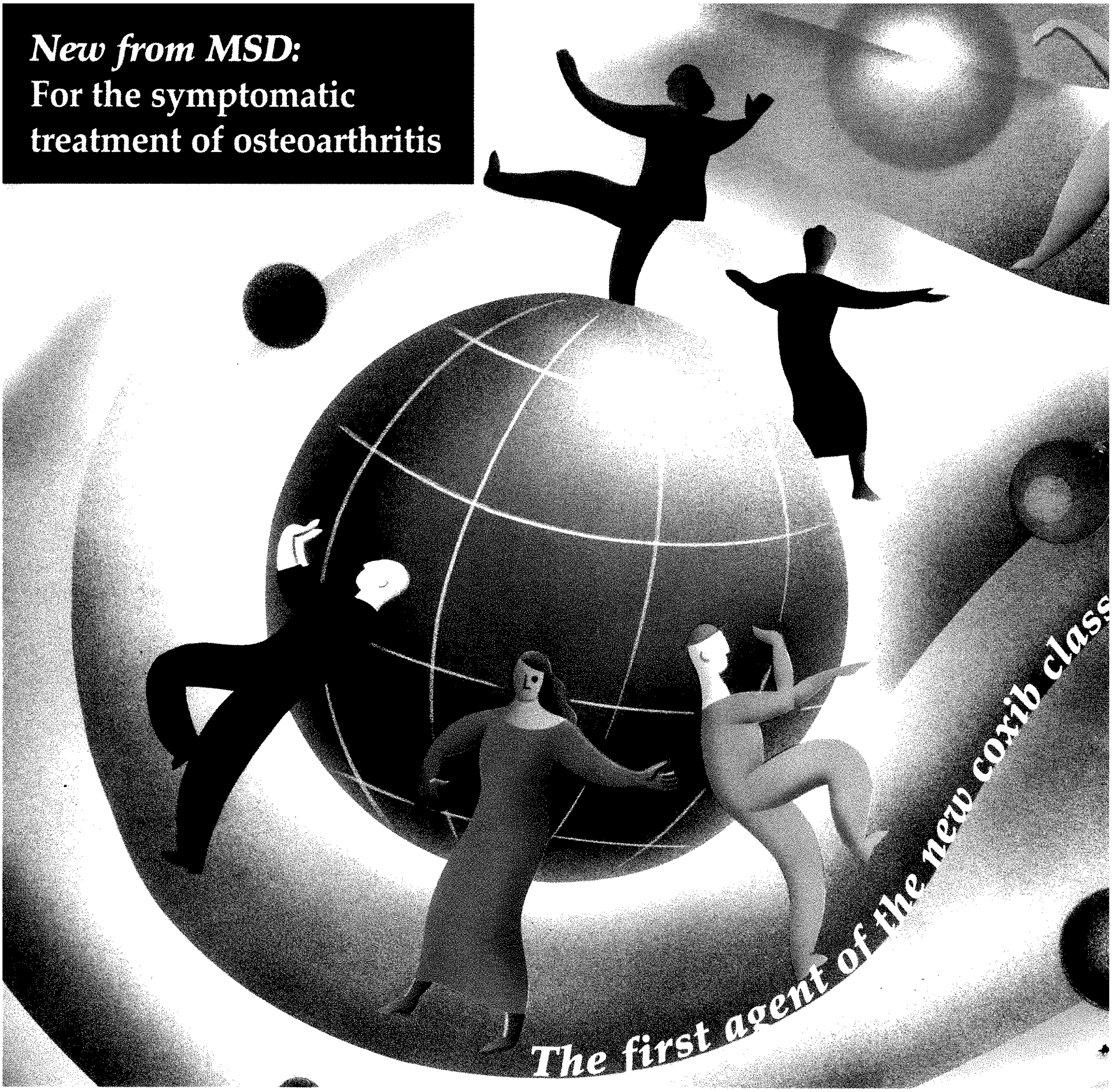
- Improved design for superior flashback[1]
- New 27G addition to range
- Available as pencil point and lancet point

SIMS Portex

For further information, please call SIMS Portex on +44 (0) 1303 260551. SIMS Portex Limited, Hythe, Kent, CT21 6JL, UK.
E-mail: info@portex.com

[illegible]

SIMS
SMITHS INDUSTRIES
Medical Systems
INNOVATION IN CRITICAL AND COMMUNITY CARE


New from MSD:
For the symptomatic treatment of osteoarthritis
The first agent of the new coxib class

VIOXX®▼ (rofecoxib) ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib.

VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

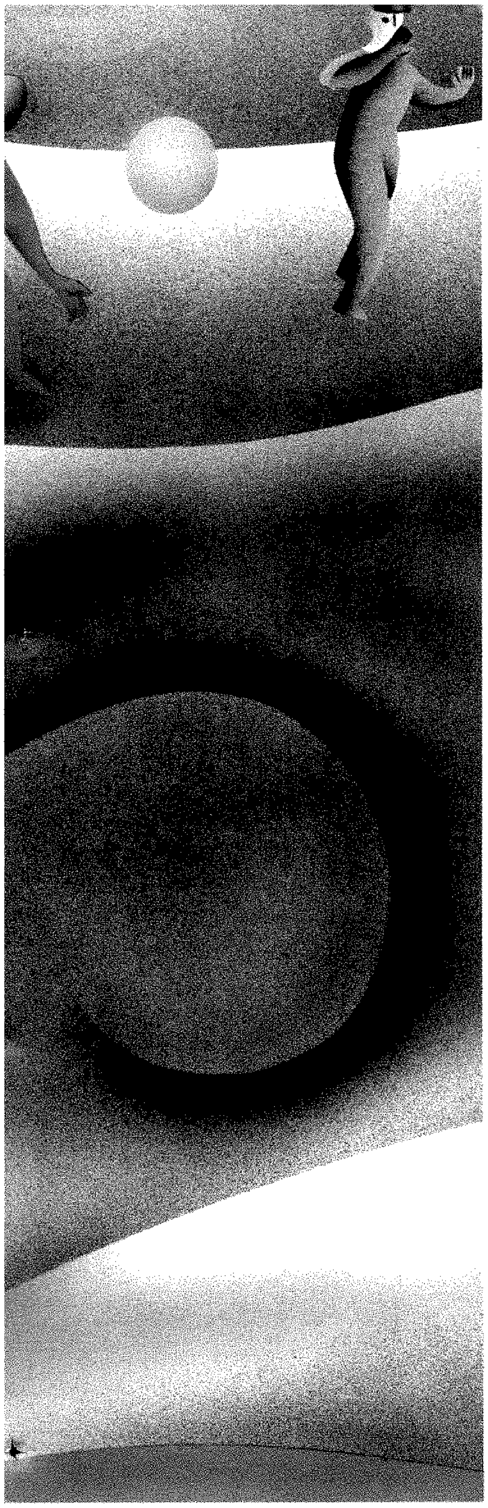
Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib.

Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone. This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1]*

- The power of high-dose NSAIDs – diclofenac and ibuprofen.[2]
- Superior GI safety profile compared to conventional NSAIDs – diclofenac, ibuprofen and nabumetone.[2,3]
- True once-daily therapy – for a wide range of patients.[2]

* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

TRUE ONCE-DAILY

VIOXX® ▼

(rofecoxib)

Selective. Strong. Simple.

rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer.

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** December 1999

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

© Merck Sharp & Dohme Limited 1999. All rights reserved.

References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Laine L, Harper S, Simon T et al. A randomised trial comparing the effect of rofecoxib, a cyclo-oxygenase-2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;117:776-783.

MSD

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

05-00 VOX.99.GB.65619.Jf

One Year Obstetric Anesthesia Fellowship

Duke University Medical Center
Durham, North Carolina, USA

Want to get further obstetric anesthesia experience/research and enjoy a good climate/lifestyle? This post is for you. The Department of Anesthesiology at Duke University Medical Center invites applications for Fellowship in Obstetric Anesthesia for the academic year beginning July 2000.

Candidates should have FRCA prior to commencing post. Emphasis on clinical research and advanced clinical training in a tertiary center with approximately 3,000 deliveries per year including many high risk consults and referrals. Opportunities to participate in NIH-funded laboratory research as well as clinical outcomes research. Salary $45,000/annum.

Applicants should send a curriculum vitae and 3 letters of reference to Elizabeth Bell, M.D., M.P.H., Fellowship Director, Division of Women's Anesthesia, Department of Anesthesiology, Box 3094, Duke University Medical Center, Durham, NC 27710. Tel: (919) 681-6535, Fax: (919) 681-8357, E-mail: bell0027@mc.duke.edu

Informal discussion encouraged with either Elizabeth Bell, M.D.; or John Booth, M.B., Ch.B., FRCA, E-mail: booth006@mc.duke.edu

---

McMaster University
Hamilton, Canada

Cardiac Anaesthesia Fellowship

Applications are invited for a Cardiac Anaesthesia Fellowship at Hamilton Health Sciences Corporation, a tertiary regional cardiac centre serving an area from the Niagara Pennisula to the Bruce Peninsula as well as Northwestern Ontario. Annual cardiac surgical volume is over 1,300, providing a full range of cardiac surgical procedures.

Further information is available on the website:

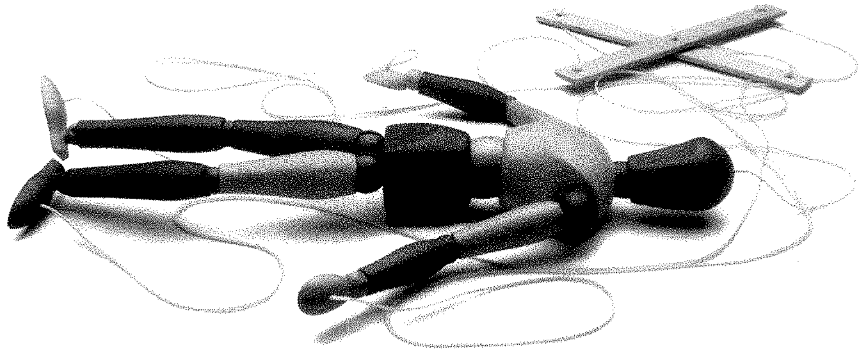
http://www-fhs.mcmaster.ca/anaesthesia/education
or from Mrs Mary Gahagan, Office of the Chair,
Department of Anesthesia, McMaster University,
HSC-2U1, 1200 Main St W, Hamilton,
Ontario, Canada L8N 3Z5
Tel: 01-905-521-2100 ext. 75166
Fax: 01-905-523-1224
E-mail: gahaganm@fhs.mcmaster.ca

ESMERON

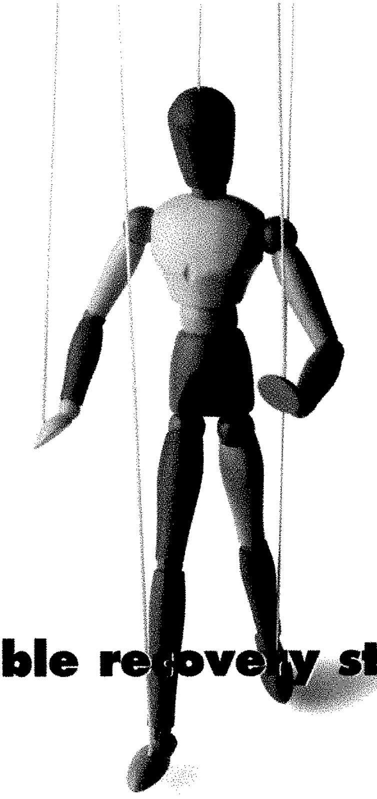
Presentation: 10 mg/ml rocuronium bromide in 5ml or 10ml vials as an aqueous solution for injection. **Other ingredients:** sodium acetate, sodium chloride, acetic acid to pH 4 and water for injections.
Uses: As an adjunct to general anaesthesia to facilitate endotracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.
Dosage and administration: Esmeron is administered intravenously as a bolus or as an infusion. See Summary of Product Characteristics for compatibilities.
Dosage is individualized taking into account method of anaesthesia, duration of surgery, possible interactions with other drugs and the patient's condition. Routine use of appropriate neuromuscular monitoring technique is recommended.
In adults: For short to long lasting surgical procedures:
Intubation: 0.6 mg / kg, Rapid sequence induction 1.0mg/kg,
Maintenance dose: 0.15 mg/kg, (reduce to 0.075mg - 0.1mg/kg for Long-term inhalational anaesthesia).
Continuous infusion: Loading dose 0.6 mg/kg, then infusion rate 0.3 - 0.6 mg/kg/hour or under inhalational anaesthesia 0.3 - 0.4mg/kg/hr. Continuous monitoring of block is essential.
(See Summary of Product Characteristics for advice for intensive care procedures, children, elderly, cirrhotic and overweight patients).
Contraindications Previous anaphylactic reactions to rocuronium or the bromide ion.
Precautions and warnings: Use under the supervision of experienced clinicians familiar with neuromuscular monitoring techniques. Ventilation is mandatory until adequate spontaneous respiration is restored. Dose levels above 0.9 mg/kg may increase heart rate which could counteract bradycardia produced by other anaesthetic agents or vagal stimulation. Hepatic and/or biliary tract disease, renal failure, prolonged circulation time and neuromuscular disease hypothermia and obesity may influence the effects of Esmeron. Severe electrolyte disturbances, altered blood pH or dehydration should be corrected when possible. Clinicians should be aware of the signs and symptoms of malignant hyperthermia
Effect on ability to drive or use machines: Using potentially dangerous machinery or driving are not recommended within 24 hours of full recovery.
Use in pregnancy and lactation: Esmeron should be given to pregnant or lactating women only when the benefits outweigh the risks. Dose in Caesarean section: 0.6mg/kg.
Side effects: Anaphylactic reactions are very rarely seen. No clinically significant tachycardia, hypotension or other clinical signs of histamine release have been reported.
Interactions: Other drugs may influence the effects of non-depolarizing NMBA's, including anaesthetics, other NMBA's, antibiotics and suxamethonium, diuretics, (-adrenergic blocking agents. See Summary of Product Characteristics for details.
Overdose: The patient should continue to be ventilated. When reversal fails ventilation must be continued until spontaneous breathing occurs.
Other Information: A dose of 0.6 mg/kg provides adequate intubation conditions within 60 seconds in nearly all patients, with a clinical duration of 30-40 minutes. General muscle paralysis is established within 2 minutes.
Package quantities: 50mg/5ml (12 vials) 100 mg/10ml (10 vials).
NHS Prices 50mg x12 vials - £38.78 100mgx10 vials - £64.63 Legal Category POM Product Licence Number 3524/0025
Further information is available from Organon Teknika Limited, Cambridge Science Park, Milton Road, Cambridge CB4 OFL

Oct 1999

organonteknika Boseind 15, 5281 RM Boxtel, The Netherlands, tel. +31 (0) 411 65 49 11, fax +31 (0) 411 65 42 01
http://www.organonteknika.com



Rapid relaxation gets the applause...



...then predictable recovery steals the show.

An outstanding safety profile in all procedures.

Esmeron has now been used with confidence in over 35 million patients. This confidence is the result of its outstanding clinical profile:

Rapid onset

Esmeron at a dose of 0.6 mg/kg ensures control of the airway within one minute in 95% of patients. Its onset time is faster than that of all available non-depolarizing neuromuscular blocking agents.[1]

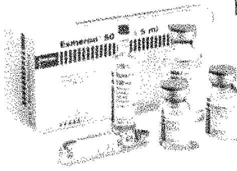
Predictable recovery

Esmeron's spontaneous recovery index is relatively constant, following either single or multiple bolus doses or after use as a long-lasting intravenous infusion.[2, 3]

Stable hemodynamic profile

"In contrast to atracurium, mivacurium and tubocurarine, administration of Esmeron caused no significant changes in plasma histamine concentrations or in hemodynamic state at any time."[4]

For full details of this exceptional all-rounder, please contact your local Organon Teknika representative.

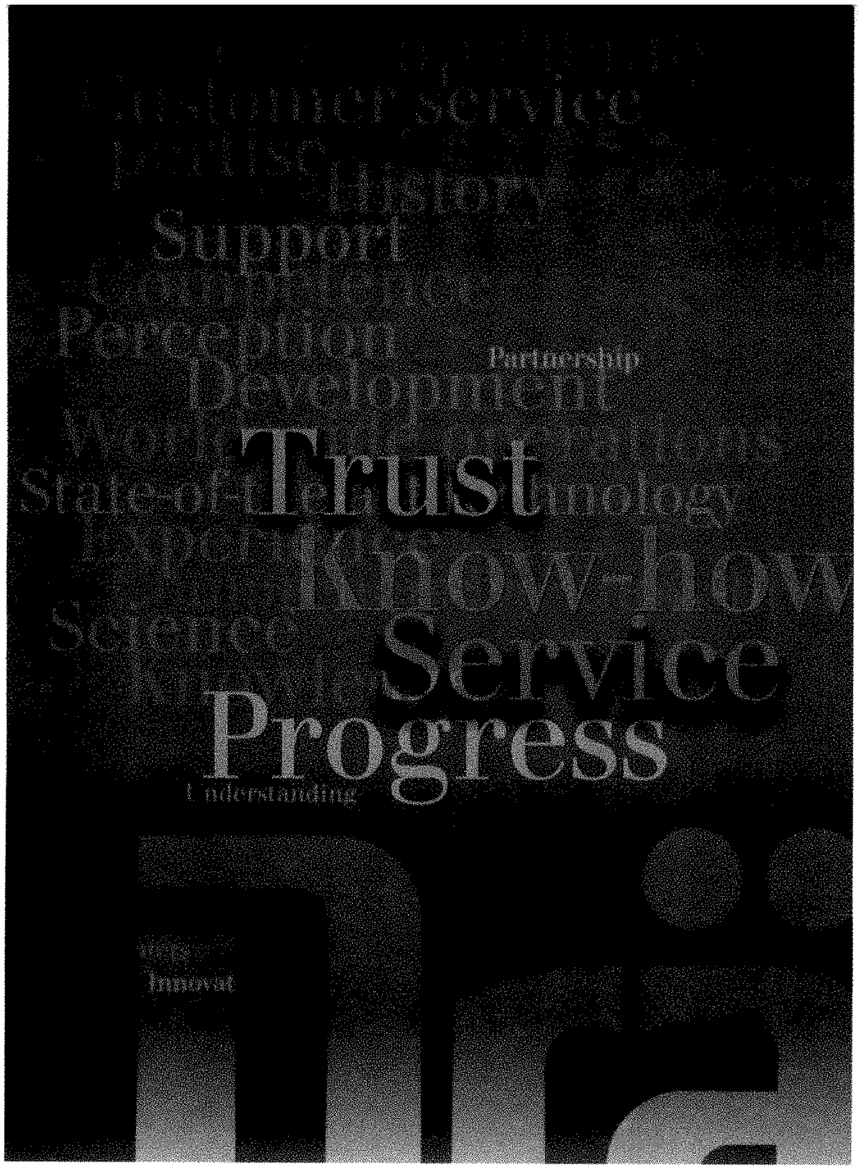


1. Puhringer et al. Anesth. Analg. 1992; 75: 37 - 40 **2.** Foldes et al. Exc Med Ams. 1990: 171 - 181 **3.** Sparr et al. Eur J Anaesth. 1994: 11(9): 63 - 65 **4.** Naguib et al. Br J Anaesth. 1995; 75: 588 - 592

organonteknika

ESMERON®
ROCURONIUM BROMIDE

For more information: Organon Teknika bv, Boseind 15, 5281 RM Boxtel, telefoon +31 (0)411 654911, telefax +31 (0)411 654201



Dräger

For years, your choice

has kept us on top.

This has only been possible

through dialogue and

a spirit of partnership with you. And yet, we especially value varying standpoints. We aim to continue this dialogue with you in the future and will do our best to keep you, our customer, satisfied. Dräger Medizintechnik GmbH, Tel. ++451 882-2020, Fax ++451 882-3374, http://www.draeger.com

Your views are important to us

PATIENT CARE ALLIANCE

Dräger. Technology for life.

Editorial Notices

8th Annual Congress of the European Society of Anaesthesiologists

Vienna, Austria, April 1–4, 2000

The congress will be held in the Austria Center.

Abstract deadline is December 1, 1999.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Diagnostic Imaging of the Shoulder, Elbow and Wrist Joints: A Radioclinical Challenge

Genval (Brussels), April 28–29, 2000

The symposium is sponsored by the GETROA (Groupe d'Etude et de Travail en Ostéo-Articulaire). The specific aims of the symposium are: to summarize the current state of knowledge on shoulder, elbow and wrist imaging using state-of-the-art techniques; to establish consensual algorithmic approaches for diagnosing of upper extremity pathology, formulating on this basis recommendations to the medical community; to discuss unsolved clinical problems and potential solutions based on current clinical and imaging knowledge; and to explore future directions of investigations.

December 31, 1999 (deadline for submission of abstracts).

For further information, please contact:

F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium.

Tel: +32 2 555 68 44; Fax: +32 2 520 35 56; E-mail: fschuind@ulb.ac.be

Final FRCA Course

Leicester, May 2–5, 2000

The course will take place at Glenfield Hospital, Leicester and includes lectures, tutorials, mock vivas, mock examinations and video-recorded vivas.

Places are limited so please apply early.

Course fees: £220.00

For further information please contact:

Mrs C. Gethins, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Tel: +44 116 258 5291; Fax: +44 116 285 4487; E-mail: chg2@le.ac.uk. Details also on departmental web page: www.le.ac.uk/anaesthesia.

German Congress of Anaesthesiology 2000

Munich May 6–9, 2000

For further information, please contact:

Nadja Schwarz, Project Managment, Medizinische Congressorganisation Nürnberg GmbH, Wielandstraße 6, D-90419 Nürnberg, Germany.
Tel: +49 911 39 3160; Fax: +49 911 33 1204; E-mail: mcn@mcn.nuernberg.de
www:http//www.mcn-nuernberg.de

5th Congress of the European Resuscitation Council 'Resuscitation 2000'

Antwerp, June 1–3, 2000

Congress Director: Prof. Dr Leo Bossaert

For further information, registration and abstracts, please contact:

ERC secretariat, PO Box 113, 2610 Antwerp, Belgium.

Tel: +32 3 821 36 16; Fax: +32 3 828 48 82; E-mail: erc@uia.ua.ac.be; Website: http://www.erc.edu.

For hotel reservation and tours, contact:

Medicongress, Waalpoel 28/34, 9960 Assenede, Belgium.

Tel: +32 9 344 39 59; Fax: +32 9 344 40 10; E-mail: ERC2000@medicongress.com; Website: http://www.medicongress.com/erc.

*Pre-congress courses in BLS, AED, ALS, PLS on May, 29–31, 2000.

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

World Paediatric Anaesthesia Meeting

Nova Scotia June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

Edinburgh Anaesthesia Festival

Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 (0)131 536 3652; Fax: +44 (0)131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl.

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.

Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)

Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

ESA

EUROPEAN SOCIETY
OF ANAESTHESIOLOGISTS

AUSTRIAN SOCIETY
OF ANAESTHESIOLOGY
RESUSCITATION AND
INTENSIVE CARE MEDICINE

ÖGARI

IN COOPERATION WITH
THE EUROPEAN ACADEMY OF
ANAESTHESIOLOGY

JOIN US IN
VIENNA
1-4 APRIL
2000

8th ESA
Annual Meeting
with the Austrian
International
Congress

Symposia, Refresher Courses, Workshops, Industrial Symposia and Exhibition,
Free Presentations (oral and poster discussions)

English and German language sessions

ESA SECRETARIAT
32 AV. DE TERVUREN - BTE 30
B-1040 BRUXELLES BELGIUM
PHONE +322 743 32 90
FAX +322 743 32 98
E-MAIL: esa@euronet.be
WEB: www.euroanesthesia.org

ÖGARI SECRETARIAT
JOH. NEPOMUK VOGL-PLATZ 1
A-1180 VIENNA AUSTRIA
PHONE: +431 406 48 10
FAX: +431 406 48 11
E-MAIL: oegari@oegari.at
WEB: www.oegari.at

Deadline
abstracts:
October 15,
1999

AMA Category I
CME Accreditation

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)

Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 – September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.
Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org

ISMETT*

HEART/LUNG TRANSPLANT ANESTHESIA AT UPMC PALERMO

**(l'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione)*

The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government to be inaugurated during 2000. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@ anes.upmc.edu

SOCIETY FOR AIRWAY MANAGEMENT

ANNUAL SOCIETY MEETING
WITH HANDS-ON WORKSHOPS

JUNE 2 – 4, 2000

LOEWS LE CONCORDE
Quebec City, Canada

Ulrich Braun, M.D., President
Program Chairman, D. John Doyle, M.D., Ph.D.

The Society For Airway Management (SAM) has been formed with the charter of improving airway management in adults and pediatrics, through research and education. Anesthesiologists, critical care specialists, emergency medicine physicians, otolaryngologists and CRNA's should attend. All aspects of the difficult airway will be covered including special cases pertinent to otolaryngologists and emergency medicine physicians. Hands-on workshops, taught by members of the distinguished faculty, will include training in the following: Adult & Pediatric Fiberoptic Intubation, Lung Isolation, Rigid Fiberoptic Laryngoscopy, Direct Laryngoscopy, Tracheal Light Wand, COPA, LMA, Airway Nerve Block, Combitube and VETT, Cricothyrotomy and Jet Ventilation, Retrograde Intubation, Rigid Bronchoscopy, Rigid Laryngoscopy and Airway Tube Exchangers. For more information or brochure contact:

MMC/UCI Center for Health Education
2801 Atlantic Avenue
Long Beach, CA 90806
(562) 933-0100 or
(562) 933-0101 FAX / britchie@memorialcare.org

Meeting Announcement

TEMPERATURE AND ACUTE CARE

Thursday, 29 June 2000
Rupert Beckett LectureTheatre, University of Leeds, Leeds LS2 9JT

Chaired by: Dr Mahesh Shah

PROGRAMME TOPICS

Thermoregulation and Anaesthesia
Dr Charles Deakin, Southampton

Effects of Temperature Changes on Organ Systems
Dr Angus Crossley, Derby

Temperature Regulation in the Critically ill Patient
Dr Andrew T Cohen, Leeds

Techniques to Regulate and Measure Temperature
Dr Glynn Baxendale, Nottingham

Temperature Care in the Accident and Emergency Dept
Mr Paul Grout, Hull

Does Warming Therapy Prevent Pressure Ulcers?
Ms Eileen Scott, North Tees

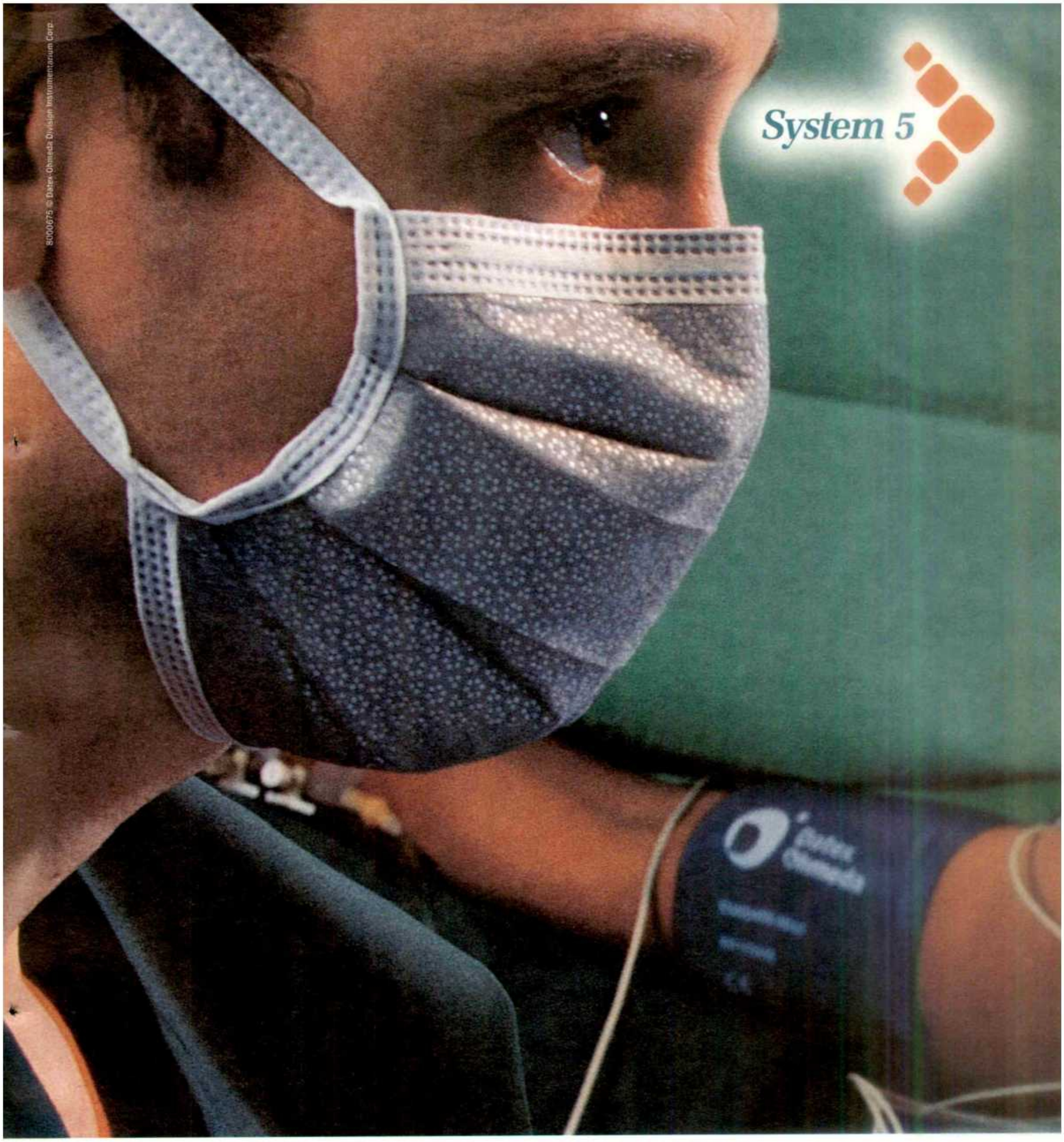
Post Surgical Wound Infections in Day Case Surgery
Mr Andy Melling, North Tees

CME approval and RCN accreditation has been applied for

Registration Fee: £60.00 medical; £30.00 non-medical

SUPPORTED BY AN EDUCATIONAL GRANT FROM ACTAMED

Please contact : Maxine Playford, Dept of Anaesthesia, Leeds General Infirmary, Great George Street, Leeds LS1 3EX.
Tel: 0113 392 6345. Email:maxinep@ulth.northy.nhs.uk



Soft landing

They say anesthesia is like flying an airplane.
Taking off and landing are the riskiest phases.
Landing your patient softly in recovery
will never be routine.

Datex·Ohmeda

Devoted to caring for life

ANAESTHESIA AND INTENSIVE CARE

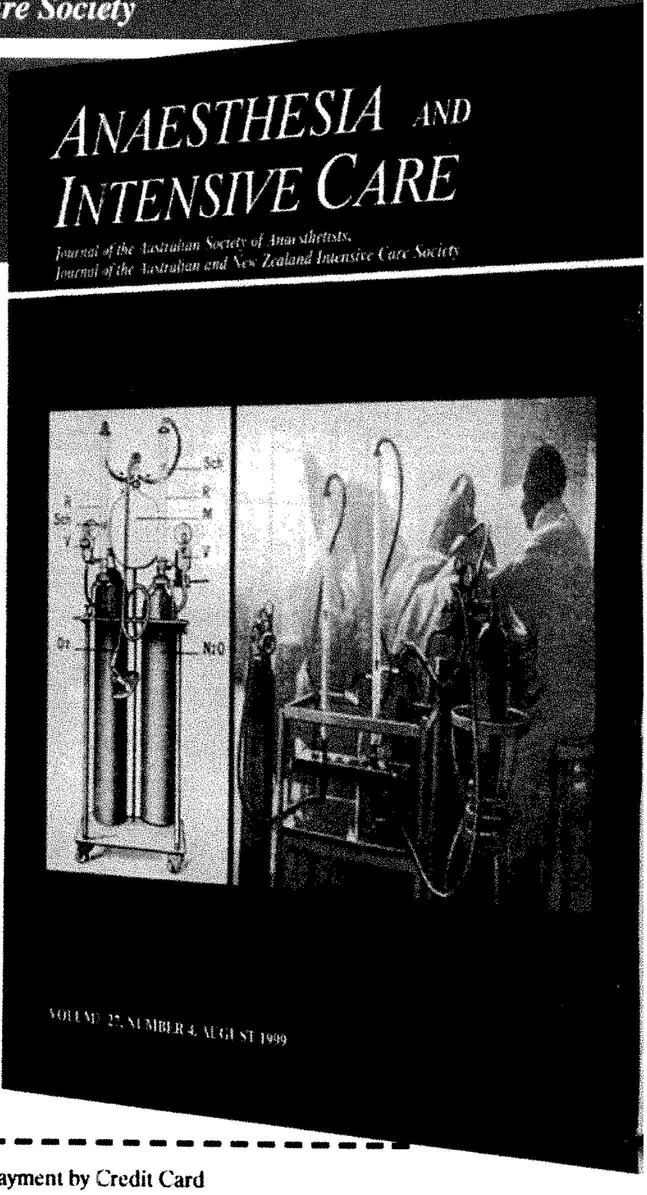
Journal of the Australian Society of Anaesthetists,
Journal of the Australian and New Zealand Intensive Care Society

Chief Editor; Editor Anaesthesia: **John G. Roberts**
Editor; Intensive Care: **Alan W. Duncan**
Executive Editor: **Jeanette Thirlwell Jones**
Assistant Editor: **Ian M. McKenzie**
Assistant Editor: **Michael J. Paech**

ANAESTHESIA AND INTENSIVE CARE is a bi-monthly publication presenting original articles of scientific and clinical interest in the specialties of Anaesthesia, Intensive Care, Pain Therapy and related disciplines.

Frequent symposium issues, comprehensive review articles, dissertations on the history of anaesthesia and education and training in these specialties are informative and authoritative. It contains lively Correspondence and comprehensive Book Review Sections, Future Meetings and courses of interest to anaesthetists. The Journal is international in content and readership.

Official Journal of the Australian Society of Anaesthetists, and the Australian and New Zealand Intensive Care Society.


ANAESTHESIA AND INTENSIVE CARE
Journal of the Australian Society of Anaesthetists, Journal of the Australian and New Zealand Intensive Care Society
VOLUME 27, NUMBER 4, AUGUST 1999

SUBSCRIPTION RATES 2000 - 6 ISSUES PER YEAR

AUSTRALIA:		ALL OTHER COUNTRIES	
Individual	$132	Individual	$175
Institutional	$180	Institutional	$298

(Includes GST from 1st July 2000)

All amounts are specified in Australian Dollars.
The Journal is airmailed to all destinations outside Australia.

ORDER FORM

I wish to subscribe to *ANAESTHESIA AND INTENSIVE CARE* for one year:

- ☐ I enclose cheque/money order/bank draft
- ☐ Please charge credit card

Name: ....
Address: ....
....
....
Post/Zip code: ....

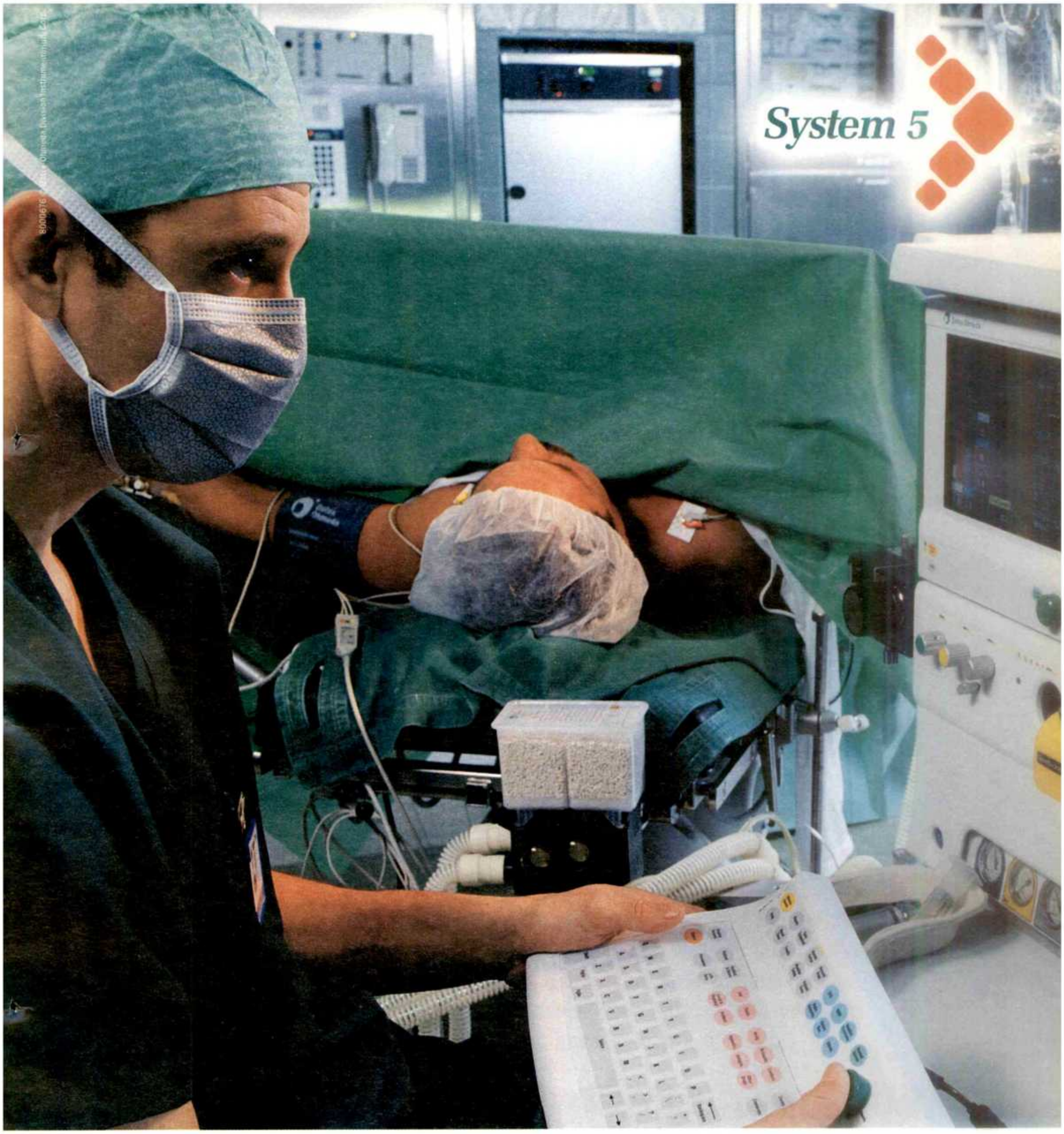
Payment by cheque: Please make cheque payable to *ANAESTHESIA AND INTENSIVE CARE*

Payment by Credit Card

☐ Visa ☐ Mastercard ☐ American Express

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Purchase Order No: ....
Amount paid: $ ....
Card Holder's Name: ....
Signature: ....
Expiry Date: ....

Mail Applications to:
Subscriptions
ANAESTHESIA AND INTENSIVE CARE
PO Box 600
Edgecliff NSW 2027 Australia
Ph 61.2.9327 4022 Fax 61.2.9362 9139
Email: aicsec@ozemail.com.au



New awakening

System 5 is Datex-Ohmeda's new product family. It holds everything we know about anesthesia and critical care. From pre-operative assessment to recovery.

Contact your nearest Datex-Ohmeda partner. Let's discuss System 5 and new opportunities.

Datex·Ohmeda

Devoted to caring for life

GERMAN CONGRESS OF ANAESTHESIOLOGY

DAK International

DAK 2000
MÜNCHEN

May 6th – 9th, 2000

Internationales
Congress Center Munich

Information:

MCN MEDIZINISCHE CONGRESS-
ORGANISATION NÜRNBERG **AG**
Zerzabelshofstrasse 29 • 90478 Nürnberg, Germany
☎ ++49(0)911/393160 • FAX ++49(0)911/331204
e-mail: mcn@mcn-nuernberg.de • www: http://www.mcn-nuernberg.de

---

FREE e-mail alerting service

• •

All Oxford University Press journals offer an e-mail table of contents alerting service. You can join this to be sent the table of contents of each issue of this journal (and any other OUP journal that you select). To register, simply go to: www.oup.co.uk/jnls/tocmail, select the OUP journal/s of your choice, and enter your e-mail address to register for this free service.

stay ahead of the field

Make sure you're among the first to read the very latest research and review papers.

save time

You can browse the table of contents, and then visit the web site to read the abstracts of any papers which catch your interest, all without leaving your desk!

keep informed

You can quickly see what papers are being published across a wide range of topics.

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 84, Number 3, March 2000

Editorial I

Postoperative residual curarization and evidence-based anaesthesia

In this issue of the journal, Baillard and colleagues[1] report the results of an investigation of the incidence of postoperative residual block in the recovery room after routine use of vecuronium without the use of a nerve stimulator and without reversal. The results are alarming: clinically significant residual block (TOF <0.7) was found in 42% of a total of 568 patients, and in 33% of 435 patients who were extubated before arrival in the recovery room.

As with all unexpected and disquieting results questioning apparently accepted long-standing clinical practice, many clinicians will undoubtedly deny them and start criticizing the study. And certainly, it is open to criticism for many reasons, of which some of the most important are: the clinical criteria used for evaluating recovery of neuromuscular block are not given and nor is the number of patients receiving more than one dose of vecuronium; the duration of anaesthesia and TOF ratios found in the recovery room are not available, making impossible an evaluation of the relationship between duration of anaesthesia and incidence and severity of residual block; the data are obviously not normally distributed and are presented in a way (mean (SD)) that makes it very difficult, if not impossible, for the reader to evaluate the results further; and finally, many anaesthetists would claim that failure to antagonize medium-duration non-depolarizing neuromuscular blocking agents in the absence of monitoring is not acceptable practice in these days of evidence-based medicine, and that the study is therefore redundant and irrelevant. The fact is however, that there are international differences in practice, and that the technique described in this study is still used throughout the world. The message is clear: if you do not monitor or antagonize vecuronium-induced neuromuscular block, an unacceptably high proportion of patients will have clinically significant residual block in the recovery room, a finding that most probably also applies to the other intermediate- and long-acting neuromuscular blocking agents.[2–6]

What is good evidence-based practice?

Let us first examine the criteria for sufficient postoperative recovery of neuromuscular function. For many years, a train-of-four (TOF) ratio of 0.7, measured at the thumb, was considered to reflect adequate recovery.[7] However, recent studies have documented that this TOF ratio does not guarantee clinically sufficient recovery. Eriksson and colleagues[8 9] have shown convincingly that at this TOF ratio, chemoreceptor sensitivity to hypoxia is decreased, leading to insufficient ventilatory response to hypoxia The same group showed that a TOF ratio ≤ 0.7 is associated with functional impairment of the muscles of the pharynx and upper oesophagus, predisposing to regurgitation and aspiration [10] In accordance with this, it has been documented that a TOF ratio ≤ 0.7 is a risk factor for development of postoperative pulmonary complications.[11] According to the findings of Eriksson and colleagues[8–10 12] and those of Kopman, Yee and Neuman,[4] normal vital muscle function, including normal pharyngeal function, requires the TOF ratio at the adductor pollicis to recover to ≥ 0.90.

How do we then, at the end of anaesthesia, ensure sufficient recovery of neuromuscular function?

First, it is important to realize that whether a TOF ratio of 0.9, 0.8 or even 0.7 is taken to reflect sufficient recovery, it is not possible either by clinical evaluation[13] or tactile or visual evaluation of the response to peripheral nerve stimulation to exclude clinically significant residual paralysis.[13–17] What is possible is to decrease the frequency and severity of residual block by tactile evaluation of the response to nerve stimulation[16 17] and probably also by performing relevant clinical tests correctly (Table 1). However, in daily clinical practice, these methods do not secure against residual block.[13–17] The clinical tests are often not performed correctly, and tactile or visual evaluation, or both, of the response to peripheral nerve stimulation is not sensitive enough to exclude residual block.[15 18 19] Often even experienced observers cannot feel fade if the TOF ratio has recovered to more than 0.4,[18 19] and sometimes inexperienced observers do not feel fade when TOF ratios are as low as 0.1–0.2.[15] In daily clinical practice, significant residual block can be excluded with certainty only if more objective methods of monitoring are used, such as mechanomyography, electromyography or acceleromyo-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Clinical tests of postoperative neuromuscular recovery

Unreliable	
	Sustained eye opening
	Protrusion of the tongue
	Arm lift to opposite shoulder
	Normal or near normal vital capacity
	Maximum inspiratory pressure ≤ -25 cm H_2O
Reliable	
	Sustained head lift for 5 s
	Sustained leg lift for 5 s
	Sustained hand grip for 5 s
	Sustained tongue depressor test[4]
	Maximum inspiratory pressure ≥ -50 cm H_2O

graphy.[20] Ideally, clinicians should *always* quantitate the extent of neuromuscular recovery using one of these methods. At a minimum, the TOF ratio should be measured during recovery whenever a non-depolarizing neuromuscular block is not antagonized, and the response to nerve stimulation should always be considered in relation to reliable clinical signs and symptoms of residual block (Table 1).

Most likely, the above guidelines seem unnecessarily rigorous and unrealistic to many anaesthetists. Nevertheless, evidence-based medicine is the use of the best available evidence in making decisions about the case of individual patients, and the above guidelines reflect exactly that.

The ideal world is one thing, the real world another! In many departments, clinicians do not have access to equipment for measuring the degree of neuromuscular block. How then do we evaluate and, as far as possible, exclude residual postoperative block? First, long-acting neuromuscular blocking agents should not be used.[3 11] Second, the block should be antagonized at the end of the procedure, but reversal should not be initiated before two and preferably three or four responses to TOF stimulation are present. Third, if a nerve stimulator is available, tactile evaluation of response to double-burst stimulation (DBS) is preferred over tactile evaluation of the response to TOF stimulation during recovery because it is easier to feel fade in the DBS than in the TOF response.[17 21] Finally, the clinical signs and symptoms of residual block should be considered in relation to the response to nerve stimulation.

If a nerve stimulator is not available, antagonism should not be attempted unless spontaneous muscle activity is present. Also, knowledge of and meticulous adherence to the rules for clinical evaluation of residual block is mandatory (Table 1). However, as mentioned previously, routine use of clinical tests does not always exclude significant residual block. Every operating room and recovery room should therefore have an apparatus for recording evoked responses. Whether the function of this apparatus is based on mechanomyography, electromyography or acceleromyography is not crucial, as long as the clinician knows how to use the apparatus in question.

In summary, the study by Baillard and colleagues[1] clearly documents that it is not good evidence-based practice to neither monitor nor antagonize an intermediate-acting neuromuscular blocking drug, and that routine clinical evaluation of recovery of neuromuscular function does not exclude clinically significant residual curarization. Good evidence-based practice dictates that much more attention should be paid by anaesthetists to the problems of residual curarization. At a minimum, the clinician should always monitor the extent of neuromuscular recovery using objective means, whenever non-depolarizing neuromuscular block is not antagonized.

J. Viby-Mogensen
Department of Anaesthesia
Copenhagen University Hospital
H:S Rigshospitalet
Blegdamsvej 9, 2100 København
Denmark

References

1 Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; **84**: 394–5

2 Viby-Mogensen J, Jørgensen BC, Ørding M. Residual curarization in the recovery room. *Anesthesiology* 1979; **50**: 539–41

3 Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. *Anesthesiology* 1988; **69**: 272–6

4 Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers *Anesthesiology* 1997; **86**: 765–71

5 Gordon KL, Reilly CS. Recovery of neuromuscular function after infusion or intermittent bolus doses of atracurium or vercuronium. *Br J Anaesth* 1989; **62**: 269–73

6 Fawcett WJ, Dash A, Francis GA, Liban JB, Cashman JN. Recovery from neuromuscular blockade: residual curarisation following atracurium or vecuronium by bolus dosing or infusions. *Acta Anaesthesiol Scand* 1995; **39**: 288–93

7 Ali HH, Utting JE, Gray C. Quantitative assessment of residual antidepolarizing block (part II). *Br J Anaesth* 1971; **43**: 478–85

8 Eriksson LI, Lennmarken C, Wyon N, Johnson A. Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. *Acta Anaesthesiol Scand* 1992; **36**: 710–15

9 Eriksson LI, Sato M, Severinghaus JW. Effect of a vecuronium-induced partial neuromuscular block on hypoxic ventilatory response. *Anesthesiology* 1993; **78**: 693–9

10 Eriksson LI, Sundman E, Olsson R, *et al.* Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. *Anesthesiology* 1997; **87**: 1035–43

11 Berg H, Viby-Mogensen J, Roed J, *et al* Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41**: 1095–103

12 Eriksson LI. The effects of residual neuromuscular blockade and volatile anesthetics on the control of ventilation. *Anesth Analg* 1999; **89**: 243–51

13 Beemer GH, Rozental P. Postoperative neuromuscular function. *Anaesth Intensive Care* 1986; **14**: 41–5

14 Hutton P, Buchett KR, Madden AP. Comparison of recovery after neuromuscular blockade by atracurium or pancuronium. *Br J Anaesth* 1988; **60**: 36–42

15 Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engbæk J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? *Anesthesiology* 1990; **73**: 835–9

16 Shorten GD, Merk H, Sieber T. Perioperative train-of-four monitoring and residual curarization *Can J Anaesth* 1995; **42**: 711–15

17 Fruergaard K, Viby-Mogensen J, Berg H, El-Mahdy AM. Tactile evaluation of the response to double burst stimulation decreases, but not eliminates, the problem of postoperative residual paralysis. *Acta Anaesthesiol Scand* 1998; **42**: 1168–74

18 Viby-Mogensen J, Jensen NH, Engbæk J, Ørding H, Skovgaard LT, Chæmmer-Jørgensen B. Tactile and visual evaluation of response to train-of-four nerve stimulation. *Anesthesiology* 1985; **63**. 440–3

19 Saddler JM, Bevan JC, Donati F, Bevan DR, Pinto MB. Comparison of double-burst and train-of-four stimulation to assess neuromuscular blockade in children. *Anesthesiology* 1990, **73**: 401–3

20 Mortensen CR, Berg H, El-Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. *Acta Anaesthesiol Scand* 1995, **39**: 797–801

21 Drenck NE, Ueda N, Olsen NV, *et al.* Manual evaluation of residual curarization using double burst stimulation: A comparison with train-of-four. *Anesthesiology* 1989; **70**· 578–81

British Journal of Anaesthesia 84 (3): 304–7 (2000)

BJA

Editorial II

Neuropsychometric deficit after cardiac surgery: a new approach for a new millennium

'When addressing a problem in medicine, it is important to pose the correct question',
Alain Carpentier, Lancet 1997

Despite more than 20 yr of intensive investigation and research, neuropsychometric deficit after cardiac surgery remains a major cause of postoperative morbidity and an increasing contributor to perioperative mortality. In this issue of the journal, Arrowsmith and colleagues review our knowledge on this contentious subject.[1] They identify areas of recent improvement and offer opinion on issues of current concern in addition to matters that require further investigation and interpretation. Their task is not easy. Few other areas of contemporary clinical research have so repeatedly produced such glaringly inconsistent conclusions relating to the aetiology of any measured clinical deficit. While many of the early studies suffered from poor methodology, the majority of large single centre or multicentre investigations from the mid-1980s on, had no such failings. Most have been well structured, prospective, randomized studies with appropriate statistical interpretation, and yet their results were repeatedly at odds with each other. Views became readily polarized.

Attempts to identify contributory factors have followed two main routes. The first explores patient factors (patient characteristics and preoperative co-morbidities) while the second examines the role of the operator (surgical and anaesthetic), and equipment factors. There was little disagreement, even in the mid-1980s, that patient age and pre-existing cerebrovascular deficit were likely to be associated with an increased risk of neuropsychometric detriment. Yet it is only in the past few years that it has been possible to begin to explain these findings in the context of the neurobiology of cerebrovascular disease, and so encourage the formulation of new approaches to improve patient outcome.

As Arrowsmith and colleagues clearly identified,[1] duration of bypass and the complexity of the surgery performed (for example combined intracardiac and coronary artery procedures) have maintained a robust and consistent association with the incidence of postoperative cerebral deficit.[2] Other patient factors, however, such as pre-existing LV function or perioperative arrhythmias, or both, have a declining level of association, perhaps reflecting improvements in the early recognition and management of the failing heart.[3]

Although disputes have raged over the roles of micro- and macroemboli[4] and the relative advantages of a myriad of cardiopulmonary bypass oxygenators, nowhere perhaps is the disagreement among authors more readily evident than when considering the role of variations in cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) in the aetiology of perioperative deficit. Following Stockard and colleagues'[5] suggestion that a CPP of 50 mm Hg (mean) represented a perfusion pressure watershed, the literature has been awash with alternative hypotheses; all seem scientifically justifiable, but none is totally convincing. Arguments have been sited for high perfusion pressures[6] and for both pulsatile or non-pulsatile bypass procedures. The results are unconvincing and there remain no clear guidelines for peroperative CPP management.

The cause of maintaining adequate CBF levels is not helped by lack of an online monitor of cerebral well being. In the late 1980s, devices such as the cerebral function analysing monitor (CFAM) and compressed spectral assay analysers appeared likely to bridge this chasm, with online analysis allowing early intervention so avoiding permanent cerebral damage.[7] Unfortunately, they have failed to live up to their early promise. Near infrared spectrophotometry (NIRS) also appeared to offer much,[8] but so far has failed to deliver.[9]

Arrowsmith and colleagues[1] go on to suggest that the question of acid–base balance management at least, seems to be clear, but is it? The relative advantages of alpha-stat (where attempts to maintain a temperature-corrected pH of 7.4 are invariably associated with acceptance of significant hypocapnia at a temperature of 32°C) and pH-stat (where a Pa_{CO_2} of 4.7–6.0 kPa is maintained, even at hypothermic temperatures, normally by addition of carbon dioxide to the CPB circuit) have been explored fully, without reaching a consensus view. Stephan and colleagues[10] and Venn, Patel and Chambers[11] showed improved outcome with alpha-stat, mainly as a result of maintenance of 'normal' CBF, while Bashein and colleagues[12] were unable to show any difference in outcome between the two methods. In cases associated with deep hypothermic cardiac arrest however, pH-stat management before the onset of circulatory arrest appeared to improve neurological outcome.[13] So what sensible message can be taken from this discordancy. Can inside information provide any insight into why different research groups can reach such widely different conclusions on almost identical groups of patients?

Arrowsmith and colleagues[1] suggest that 'The importance of maintaining normocapnia before the onset of CPB was highlighted by Nevin and colleagues. .....'.[14] While this statement is not untrue, further examination of the facts begins to suggest some of the reasons as to why even subtle differences in the mode of application of almost identical

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

study procedures can lead to widely varying results. All of the patients in the above mentioned prospective study were exposed to pH-stat, although often to a varying degree. In many cardiac centres in the late 1980s pH-stat was achieved by adding approximately 5% carbon dioxide from a carbon dioxide cylinder on the anaesthetic machine. Invariably, inline carbon dioxide monitoring was not available, and the total amount of carbon dioxide added to the bypass circuit was totally at the discretion of the perfusionist. End-tidal carbon dioxide monitoring was often unavailable in cardiac theatres, with the acceptance of standard tidal volumes of approximately 7.5 ml kg^{-1}, often producing marked hypocapnia immediately before commencing CPB. Infrequent arterial blood-gas analysis before CPB merely added to the likelihood of significant hypocapnia. The onset of bypass, however, was often associated with excessive hypercapnia because of the over-enthusiastic addition of unmetered carbon dioxide to the bypass circuit by the perfusionist. Therefore, it was not, as stated by Arrowsmith and colleagues, the immediate pre-bypass hypocapnia that was implicated in producing the deficit,[1] but rather the degree of change in 'peri-onset of bypass Pa_{CO_2}' (from hypo- to hyper-). The effect of instantaneous changes from hypo- to hypercapnia in many patients were associated with dramatic increases in cerebral venous pressure, as measured by online jugular bulb pressure transducers. The combination of these higher venous pressures associated with low mean arterial pressures (onset of non-pulsatile CPB) often meant catastrophic decreases in CPP.

Patients suffering postoperative neuropsychometric deficit demonstrated the greatest carbon dioxide flux at the onset of bypass, other patients who, despite varying degrees of pre-bypass hypocapnia either remained mildly hypocapnic or were restored to normocapnia (approximating to alpha-stat) at commencement of CPB, had little evidence of postoperative deficit. The conclusion from this and other similar studies is not necessarily that alpha-stat is safer than pH-stat but rather that in situations where rigorous inline control of peroperative carbon dioxide normocapnia cannot be guaranteed, alpha-stat probably represents a safer option than pH-stat. Or to be more blunt, pH-stat practised badly represents a greater risk than alpha-stat practised to the same level of expertise.[15] As with much in medicine, it is not only the choice of technique that is important but also the skill, expertise and vigilance with which those techniques are applied.

There can be no doubt that improvements in surgical and anaesthetic techniques over the past 10–15 yr have contributed markedly to reduced mortality values. The lack of improvement, however, in the incidence of neuropsychometric deficit has continued to cause concern and has resulted in a variety of perioperative strategies designed to provide a degree of 'cerebral protection'. While this concept seems, in theory, entirely laudable, the terminology is much abused, often leading to great confusion. *Cerebral protection* can, by definition, only be provided pre-emptively. The use of physical or pharmacological measures post-insult in an attempt to reduce cerebral oxygen requirements and thereby limit the extension of any cerebral damage represents *cerebral resuscitation* and not *protection*. This discrimination is important, for although there is some evidence that cerebral protection (especially hypothermia) may reduce the degree of deficit for any given insult, there is no scientific evidence that cerebral resuscitatory measures are of any value in reducing either the incidence or extent of any residual deficit.

The implications of adopting the concepts of 'cerebral protection' are far reaching. To be effective, these strategies need to be given to all patients, regardless of co-morbidities, with the likelihood of only a small percentage of those patients either needing or benefiting from these manoeuvres The financial cost of such interventions would be extremely high, and is probably unsustainable in the present financial climate.

It is not only the cost of the chosen drugs that limits the routine use of cerebral protection, but also the more subtle drain that such strategies place on limited resources, in addition to the increased clinical risks associated with many of the more commonly used agents. A classical example of this is found in the thiopental study from the Texas Heart Institute in the 1980s.[16] The use of reasonably high-dose infusions of thiopental pre-emptively was associated with a significant reduction in the incidence of postoperative neuropsychometric deficit. What was not so immediately clear was the excessive duration of postoperative ventilation (often up to 7 days) and the high level of perioperative vasoactive support needed in the treatment group, almost certainly attributable to the use of thiopental. Both complications would be totally unacceptable in either routine cardiac or neurovascular practice in the UK. Needless to say, despite the glowing editorials that studies like these received at the time,[17] they have not been transferred into routine practice.

This is not to say that we should not exploit the value of cerebrally protective strategies, but rather that we should identify and target the high-risk patient. This applies equally to general (especially those with evidence of diffuse/ extensive neurovascular disease) as much as to cardiac surgical patients.

But who to target, and why?—and with what?

Efforts have been directed at reducing the degree of cerebral insult to which any patient is exposed. This strategy, however, makes the fundamental assumption that all patients respond in the same way to a standardized cerebral insult. We now know that this is almost certainly untrue.

Both severe infection and vital organ ischaemia–reperfusion are well recognized triggers for host-produced cytokines. Cytokines are pleomorphic immunoregulatory peptides. Some have been found to be pro-inflammatory (e.g. tumour necrosis factor, interleukin-1 and interleukin-8) while others have anti-inflammatory roles (e.g. interleukin-

6 and interleukin-10). An increase in pro-inflammatory cytokines has been well described in a variety of critical illnesses, such as acute respiratory distress syndrome, acute traumatic brain injury, severe sepsis[18] and after cardiac surgery. In the last case, increasing evidence implicates the CPB circuitry as the source of cytokine activation.[19] In all cases, outcome was related directly to the degree of pro-inflammatory cytokine activation. Individual response is however extremely variable. An increase in anti-inflammatory cytokines has been associated with improved outcome in many cases. These findings have led investigators to adopt clinical strategies which concentrate on either reducing/avoiding pro-inflammatory stimulation or conversely, encouraging anti-inflammatory cytokine production.

There is also clear evidence of variability in individual, genotype-related susceptibility to cerebrovascular insult. Apolipoprotein E (ApoE) is a multifunctional protein with an increasingly apparent role in the neurobiology of disease. The presence of the ApoE–epsilon 4 allele is now accepted as being an early indicator of susceptibility to the development of Alzheimer's disease. In addition to disease-specific mechanisms, there has been increasing focus on its role in modulating the response of the brain to acute insult/injury. The full implications of this association remain inadequately explored, although intense investigation continues, and so far the ApoE alleles have been implicated in outcome following: traumatic brain injury;[20] intraneuronal localization of ApoE in animal stroke models; poor recovery of function after intracerebral haemorrhage; with chronic traumatic brain injury (CTBI) in boxers;[21] and recovery of neuropsychological variables after cardiac surgery.[22] In all cases, the presence of the ApoE-4 genotype significantly increased the risk of long-term cerebral deficit. Although the neurobiology of ApoE in the injured brain remains incompletely explored, there is increasing evidence to suggest neurotrophic, immunomodulatory and antioxidant effects.

Until recently, a major limitation of studies examining changes in perioperative technique has been the lack of biochemical markers allowing quantitative assessment of neuronal injury at the time of insult. Although to date there remains no prospective, randomized assessment of such markers, there is increasing support in the literature for the use of protein S100 in such a role. Protein S100 is an acidic, calcium-binding protein, found in high concentrations in glial and Schwann cells. The appearance of this protein in serum indicates both neuronal damage and increased permeability of the blood–brain barrier and appears to be closely associated with neuropsychometric deficit after cardiac surgery.[23,24]

A new approach for a new millennium

There seems no dispute that certain genotypes are more susceptible to perioperative cerebral insult while others seem to be immunologically hyperactive in response to certain triggers, such as exposure to CPB circuits. Immunological modulation of this cytokine response has been attempted with heparin-bound CPB circuits in addition to steroid pretreatment. Initial fears of excess endotoxin release with steroid pretreatment now appear unsubstantiated, and the advantages of this therapeutic intervention seem encouraging.[25] As with other models of cerebral protection, cost and associated side effects of any chosen agent probably result in their focused application in the 'high-risk' patient.

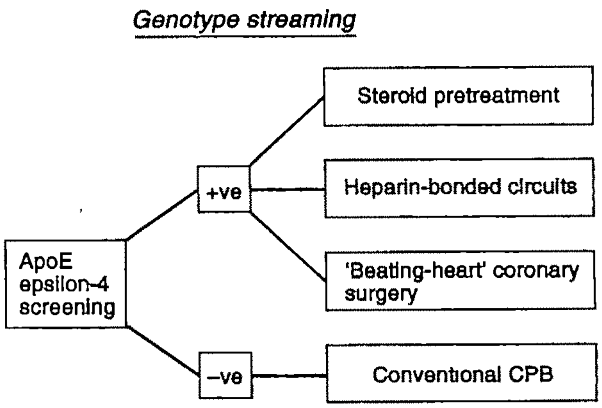


Fig 1 Preoperative genotype screening with streaming into 'normal' or 'high-risk' categories and associated peroperative bypass strategies

New operative strategies continue to evolve and therefore offer alternatives to conventional surgery. The success of 'beating heart coronary revascularization' as an alternative to CPB has been associated with a decrease in peroperative protein S100 concentrations, although evidence of a reduction in neuropsychometric deficit remains unproved.[26] In addition, this technique has been shown to be associated with a significant reduction in postoperative inflammatory activation normally associated with CPB.[27] A possible strategy may therefore involve preoperative 'genotype streaming' of patients into 'high' or 'normal' risk (Fig. 1).

However, we should have no doubts that there will be considerable resistance to such a strategy. Not least from the defenders of civil liberties, as much of this information could be potentially damaging if made available to 'life-risk' assessment agencies. Full informed consent from individual patients would be essential as would high levels of information security. Futuristic concepts of gene manipulation or gene transfer are technically within our grasp, although the moral and ethical issues that they involve represent a 'can of worms' that so far remains (for humans at least) well sealed, but for how long?

However, there is a wider audience waiting to benefit. Patients undergoing complex neurovascular surgery, whether intra- or extracranial (such as carotid endarterectomy) are at great risk of postoperative neuropsychometric deficit (as yet unmeasured). The same is true of patients with diffuse vascular disease undergoing operations associated with a high likelihood of inadvertent cerebral hypoperfusion, such as emergency aortic surgery. In all of these cases, clinical expertise and attention to detail with regards to CBF are vital, but it seems likely that only when pre-emptive intervention is tailored to individual variations in neurosusceptibility can promises of postoperative 'cerebral well being' be fully realized.

M. Nevin
Department of Anaesthesia and Intensive Care
Bristol Royal Infirmary
Marlborough St
Bristol BS2 8HW
UK

References

1 *Arrowsmith JE, Grocott HP, Reves JG, Newman MF. Central nervous system complications of cardiac surgery. Br J Anaesth* 2000; **84**: 378–93
2 Wolman RL, Nussmeier NA, Aggarwal A, *et al.* Cerebral injury after cardiac surgery: identification of a group at extraordinary risk. *Stroke* 1999; **30**: 514–22
3 Roach GW, Kanchuger M, Mora MC, *et al.* Adverse cerebral outcomes after coronary artery bypass surgery. *New Engl J Med* 1996; **335**: 1857–63
4 Blauth C, Arnold J, Kohner EM, *et al.* Retinal microembolisation during cardiopulmonary bypass as demonstrated by fluorescin angiography. *Lancet* 1986; **ii**: 837–9
5 Stockard JJ, Bickford RG, Myers RR, *et al.* Hypotension induced changes in cerebral function during cardiac surgery. *Stroke* 1974; **5**: 1974–5
6 Gold JP, Charlson ME, Williams-Russo P, *et al.* Improvements of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg* 1995; **110**: 1302–11
7 Nevin M, Colchester ACF, Adams S, Pepper JR. Prediction of neurological damage after cardiopulmonary bypass surgery. *Anaesthesia* 1989; **44**: 725–9
8 Wyatt JS, Delpy DT, Cope M, Wray S, Reynolds EOR. Quantification of cerebral oxygenation and haemodynamics in sick newborn infants by near infrared spectrophotometry. *Lancet* 1986; **ii**: 1063–5
9 Germon TJ, Evans PD, Manara AR, *et al.* Sensitivity of NIRS to cerebral and extra-cerebral oxygenation changes is determined by emitter–detector separation. *J Clin Monit Comput* 1998; **5**: 335–60
10 Stephan FC, Weyland A, Kazmaier S, et *al.* Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome. *Br J Anaesth* 1992; **69**: 51–7
11 Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg* 1995; **59**: 1331–5
12 Bashein G, Townes B, Nessly M, *et al.* A randomised trial of carbon dioxide management during hypothermic cardiopulmonary bypass. *Anesthesiology* 1990; **72**: 7–15
13 Jonas RA. Hypothermia, circulatory arrest, and the pediatric brain. *J Cardiothorac Vasc Anesth* 1996; **10**: 66–74
14 Nevin M, Colchester ACF, Adams S, Pepper JR. Evidence for involvement of hypocapnia and hypoperfusion in aetiology of neurological deficit after cardiopulmonary bypass. *Lancet* 1987; **ii**: 1493–5
15 Nevin M. Blood gas management. In: Smith P, Taylor K, eds. Cardiac *Surgery* and the Brain. London: Hodder and Stoughton, 1993; 197–215
16 Nussmeier NA, Arlund C, Slogoff S. Neuropsychometric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64**: 165–70
17 Michelfelder JD. A valid demonstration of barbiturate induced brain protection in man–at last. *Anesthesiology* 1986; **64**: 140–2
18 Cowley HC, Bacon PJ, Goode HF, *et al.* Plasma antioxidant potential in severe sepsis: a comparison of survivors and non survivors. *Crit Care Med* 1996; **24**: 1179–83
19 Wan S, LeClerc JL, Vincent JL. Inflammatory response to cardiopulmonary bypass: mechanisms involved and possible therapeutic strategies. *Chest* 1997; **112**: 676–92
20 Friedman G, Froom P, Sazbon L, *et al.* Apolipoprotein E–epsilon 4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology* 1999; **52**. 2–8
21 Jordan BD, Relkin NR, Ravdin LD, *et al.* Apolipoprotein E–epsilon 4 associated with chronic traumatic brain injury in boxing. *JAMA* 1997; **278**: 136–40
22 Roses AD, Saunders AM. ApoE, Alzheimers disease, and recovery from brain stress. *Ann N Y Acad Sci* 1997; **826**: 200–12
23 Westaby S, Johnsson P, Parry AJ, *et al.* Serum S100 protein: a potential marker for cerebral events during cardiopulmonary bypass. *Ann Thorac Surg* 1996; **61**: 42–7
24 Taggart DP, Bhattacharya K, Meston N, *et al.* Serum S-100 protein concentration after cardiac surgery: a randomised trial of arterial line filtration. *Eur J Cardiothorac Surg* 1997; **11**: 645–9
25 Wan S, LeClerc JL, Huynh CH, *et al.* Does steriod pre-treatment increase endotoxin release during clinical cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1999; **117**: 1004–8
26 Lloyd CT, Ascione R, Underwood MJ, *et al* Serum S100 protein release and neuropsychological outcome during beating heart coronary revascularisation: A prospective randomized study. *J Thorac Cardiovasc Surg* 2000 (in press)
27 Wan S, Yim APC. Why the off-pump approach reduces myocardial injury following open heart surgery. *Ann Coll Surg* 1999; **3**: 40–3

British Journal of Anaesthesia **84** (3): 308–10 (2000)

BJA

Editorial III

Placement of double lumen tubes—time to shed light on an old problem

'There's none so blind as those that won't see', Johnathan Swift 1667–1745

The ability to ventilate selectively either lung, first described by Gale in 1932,[1] represented a milestone in the development of modern anaesthetic practice. The subsequent adoption by anaesthetists of a double-lumen endobronchial tube (DLEBT) designed for differential spirometery[2] was followed by the development of numerous tubes and blockers designed to achieve one-lung ventilation (OLV). Few examination candidates can have avoided an encounter with one of these perished red rubber artefacts, usually named after its inventor. Modern lung isolation is now based largely on the use of a Robertshaw-type DLEBT—either of red rubber or polyvinylchloride (PVC) composition. A place for the more recently designed Univent tube, a polymeric silicone single-lumen tracheal tube with an attached movable bronchial blocker, is being established. Together with the development and refinement of these tubes has been a large expansion in the range of surgical procedures requiring lung isolation. In addition to lung resection, OLV is often required for spinal, aortic and oesophageal surgery.

Although now well established in anaesthetic practice, the use of DLEBT is far from problem-free. The section of the recent national confidential enquiry into perioperative deaths (NCEPOD)[3] detailing the management of patients undergoing oesophagogastrectomy makes disturbing reading. Problems with the DLEBT were a feature in 30% of deaths reported, even though patients were managed for the most part by senior anaesthetists. Problems ranged from requirement for multiple tube changes to prolonged periods of hypoxia and hypoventilation. Of particular note in the report was that 'no anaesthetist reported using a fibreoptic bronchoscope to confirm the position of the tube, either before or during surgery, even when the tube was evidently incorrectly placed'.[3]

These intraoperative ventilatory problems highlighted by the report represent the tip of a very large iceberg and demonstrate the immediate consequences of a poorly positioned tube. Another less immediate consequence of DLEBT malplacement is an increase in lower respiratory tract infections. Occlusion of a major airway, usually the right or left upper lobe bronchus, by a malplaced DLEBT promotes intraoperative lobar collapse. If this is not recognized, and the atelectatic area not re-expanded, sputum retention with secondary infection may occur after operation. Failure to achieve OLV impairs operating conditions, prolongs the procedure and necessitates protracted lung retraction with increased trauma to the manually retracted lung. A vital function of the DLEBT is protection of the dependent lung from contamination by infected secretions from the non-dependent lung. Aspiration of even a small volume of pus into the dependent lung as a result of cuff misplacement can result in severe postoperative pneumonia.[4] Forty-six percent of deaths in patients who had undergone oesophageal surgery discussed in the CEPOD report were attributed to a chest infection with subsequent development of sepsis and multi-organ failure. It is clear that a poorly placed DLEBT can compromise the patient both immediately and also in the postoperative period.

Given the serious problems with DLEBT malposition, can the procedure be made safer? With the introduction of small diameter fibreoptic bronchoscopes, it is now possible to examine the exact position of all but the smallest DLEBT, and much debate has centred on the place of routine bronchoscopy for DLEBT placement. Benumof and colleagues have argued for some time that the position of DLEBT should routinely be determined by fibreoptic bronchoscopy.[5 6] In one of the largest studies to address this issue, Klein and colleagues assessed blind insertion of plastic tubes in 200 patients.[7] Tubes were inserted by experienced anaesthetists and manipulated until the position was judged satisfactory based on clinical signs. The position was then reviewed using bronchoscopy. In 172 patients in whom placement was judged satisfactory by clinical examination and auscultation, *critical* malposition was present in 25. This increased to 48 after turning the patient to the lateral position. It is important to realize that critical malpositioning was defined as one that might affect patient safety or compromise the surgical procedure if uncorrected. Minor malposition was much more common.

There are now a large number of studies that attest to the superiority of visual inspection of the position of a DLEBT compared with the traditional use of clinical signs. Alliaume, Coddens and Deloof reported that fibreoptic bronchoscopy resulted in repositioning of 78% and 83% of blindly placed left-sided and right-sided DLEBT, respectively.[8] Smith, Hirsch and Ehrenwerth, using fibreoptic bronchoscopy, revealed that 48% of blindly placed DLEBT were malpositioned.[9] Bardoczky and colleagues, also using fibreoptic bronchoscopy, noted that 39% of blindly placed DLEBT were malpositioned.[10] Lieberman and colleagues used fibreoptic bronchoscopy to show that 83% of blindly placed left-sided DLEBT were malpositioned when the stylet was removed once the bronchial cuff had passed the vocal cords.[11] Cohen and colleagues, using fibreoptic bronchoscopy before turning the patient, found that 64%

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

and 40% of blindly placed left-sided red rubber and PVC DLEBT were malpositioned.[12] Hurford and Alfille reported that 44% of blindly placed disposable DLEBT required repositioning after fibreoptic bronchoscopy.[13] It is clear from these studies that reliance on clinical signs alone will miss a significant number of critically malpositioned tubes.

Routine use of fibreoptic bronchoscopy offers several additional benefits. The fibreoptic equipment is always available in theatre to help diagnosis and sometimes treat urgent intraoperative ventilatory problems (e.g. pneumothorax, which can be difficult to distinguish clinically from tube malplacement). Personal experience has shown that the skill of accurate and rapid tube placement becomes routine and greatly facilitates the management of rare clinical emergencies, such as bronchopleural fistula, where tube misplacement may be catastrophic. Similarly, trauma to vascular tumours, such as carcinoid, during tube placement may be avoided with bronchoscopy. Selective and atraumatic suction clearance of secretions from all major bronchi is possible, and perioperative sputum sampling can be used to guide postoperative antibiotic therapy. The availability of fibreoptic equipment in the operating theatre also promotes accurate knowledge of the anatomy of the tracheobronchial tree and familiarity with the use of an endoscope, skills that should be mandatory for the modern anaesthetic trainee.

Given this body of evidence, why then do we still see reports of blind DLEBT insertion and its consequences? It has been suggested that the use of red rubber tubes improves the success rate of blind insertion as the right upper lobe orifice of these tubes tends to be larger than that of the PVC variety.[14] The relatively large external diameter of these tubes may make distal migration less likely. Cohen and colleagues,[12] however, in a randomized comparison of PVC and red rubber tubes found that the incidence of left upper lobe occlusion was higher with the rubber variety. While Hurford and Alfille[13] suggested a higher rate of malpositions with PVC tubes, 19% of rubber tubes required bronchoscopy for initial insertion, with a further 7% requiring bronchoscopic repositioning during operation.

Central to any discussion on DLEBT placement is the fact that there is significant variation in the anatomy of the tracheobronchial tree. Further variation is added by distortion related to the presence of tumour and effusion. It is therefore not surprising that the DLEBT available have been found to be associated with a low margin of safety with respect to their potential to occlude a major airway.[5] Also important to tube stability is the relationship of the tube diameter to the bronchus to be intubated. A close match minimizes the volume of air required in the cuff and promotes stability. Unfortunately, tubes are available in a limited number of sizes and we have yet to find a reliable method of predicting the correct tube diameter for an individual patient. It should be clear then that no single tube design or construction could be expected to accommodate these anatomical variations.

The second argument for not using fibreoptic bronchoscopy may be one of cost. The initial capital outlay is significant (approximately £16 000 for a fibreoptic bronchoscope and light source) and costs (approximately £1500 annually) are incurred by servicing and repairing the equipment. Training is required, as the learning curve is steep. The additional cost per case for the frequent user may not be that high, particularly when considering the complex nature of the surgery. For the occasional user, the cost per case may seem great. We would argue that, for standards to be improved, the occasional user merits the same access to equipment and training as the routine practitioner and if this is not available, then undertaking this form of anaesthesia should be reconsidered. In purely financial terms, the very clear morbidity and mortality related to DLEBT malposition will give rise to significant expense in intensive care resources, much of which should be avoidable if fibreoptic bronchoscopy is used.

The NCEPOD report has highlighted the morbidity and mortality associated with malpositioned double-lumen tubes.[3] A fibreoptic bronchoscope should be used to place accurately a DLEBT in all patients. The position of the DLEBT should always be rechecked, and if appropriate repositioned, after moving the patient. During the procedure, further fibreoptic bronchoscopic examinations should be performed, if required, to maintain optimal DLEBT positioning and sputum clearance. Fibreoptic bronchoscopy is the only technique available to detect anatomical variability and pathological distortions and thus to ensure the accurate placement of a suitable tube (DLEBT or blockers) to achieve OLV in all patients. It is already considered the standard of care in the USA (J. Benumof, personal communication). Issues of resources, training and clinical experience[15] must no longer deflect both the large body of scientific evidence and the simple logic of visually confirming placement of every double-lumen tube. For how much longer will it be considered defensible to ignore these facts?

S. H. Pennefather
G. N. Russell
Department of Anaesthesia
Cardiothoracic Centre
Thomas Drive
Liverpool L14 3PE, UK

References

1 Gale JW, Waters RM. Closed endobronchial anesthesia in thoracic surgery. *J Thorac Surg* 1932; **1**: 432–7

2 Bjork VO, Carlens E. The prevention of spread during pulmonary resection by the use of a double-lumen catheter. *J Thorac Surg* 1950; **20**: 151–7

3 Sherry K. Management of patients undergoing oesophagectomy. In: Gray AJG, Hoile RW, Ingram GS, Sherry KM, eds. *The Report of the National Confidential Enquiry into Perioperative Deaths 1996/1997*. London: The National Confidential Enquiry into Perioperative Deaths, 1998; 57–61

British Journal of Anaesthesia **84** (3): 311–5 (2000)

BJA

CLINICAL INVESTIGATIONS

Effect of chronic intercurrent medication with β-adrenoceptor blockade or calcium channel entry blockade on postoperative silent myocardial ischaemia†

J. W. Sear[1]*, P. Foex[1] and S. J. Howell[2]

[1]*Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK.* [2]*Sir Humphrey Davy Department of Anaesthesia, University of Bristol, Bristol, UK*

**Corresponding author: Nuffield Department of Anaesthetics, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK*

We have examined observational data from four published studies investigating the incidence of postoperative silent myocardial ischaemia (post-SMI) for the effects of chronic intercurrent therapy with β-adrenoceptor blockade or chronic calcium channel entry blockade. A total of 453 patients underwent ambulatory ECG monitoring before and for 2 days after non-cardiac surgery; 79 patients were receiving chronic intercurrent β-adrenoceptor blockade and 70 calcium channel entry blockade for ischaemic heart disease or arterial hypertension. Using logistic regression analysis, we defined a model for post-SMI that included four significant terms: β-adrenoceptor blockade; calcium channel entry blockade; arterial hypertension; and vascular surgery. Using univariate regression, there was no effect of chronic β-adrenoceptor blocking therapy on post-SMI (odds ratio 0.94 (95% confidence intervals 0.54–1.65)), but there was a higher incidence of post-SMI in patients receiving chronic calcium channel entry blocking drugs (odds ratio 1.95 (1.15–3.32); $P=0.015$). There was no interaction between β-adrenoceptor blockade and calcium channel entry blockade for postoperative SMI (odds ratio 2.48 (0.71–8.73)), but there was an interaction between β-adrenoceptor blockade, calcium channel entry blockade, hypertension and vascular surgery ($P=0.0201$). These findings are at variance with those which have shown effects of preoperative β-adrenoceptor blockade on the incidence of post-SMI over the first 7 days after operation, and on mortality rates to 2 yr. There are no comparable data examining the effects of chronic intercurrent calcium channel entry blockade.

Br J Anaesth 2000; **84**: 311–5

Keywords: sympathetic nervous system, adrenergic block; calcium channel block; complications, myocardial ischaemia; heart, myocardial ischaemia; monitoring, electrocardiography

Accepted for publication. October 14, 1999

The prevalence rates of pre- and postoperative silent myocardial ischaemia (SMI) detected by ambulatory monitoring in patients undergoing non-cardiac surgery vary with the population studied; higher rates are found in those with either clinical evidence of coronary artery disease (CAD) or those with two or more risk factors for CAD. Thus in our own studies, we found that the incidence of preoperative SMI was 7.6–21.0% in patients undergoing general abdominal or vascular surgery[1–5] and 22.8–31.0% in the postoperative period.[3–5] In a recent review article, Coriat reported a preoperative incidence in predominantly vascular surgery patients of 12–28% and a postoperative incidence of 23–47%.[6]

Previous data from this department[7 8] and the recent studies of Mangano and colleagues[9] and Wallace and colleagues[10] have examined ways of reducing the incidence of myocardial ischaemia. Thus Stone and colleagues demonstrated the efficacy of a single dose of β-adrenoceptor blockade with premedication in reducing perioperative ECG changes of ischaemia (from 28% to 2%),[7] while Wallace and colleagues found that 7 days of perioperative beta-blockade with atenolol

---

†Presented in part at the Anaesthetic Research Society, London Meeting, November 19–20, 1998 (*Br J Anaesth* 1999; **82** 457–8P)

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

given either by slow i.v. infusion over 15 min or orally, reduced the incidence of SMI over the first 7 days after operation (17% *vs* 34% over the first 2 days after operation (P=0.008) and 24% *vs* 39% over the first 7 days after operation (P=0.03)).[10]

In this study, we have retrospectively examined data from four observational studies of perioperative ambulatory ECG recording (aECG) from Oxford[3 4 5 11] to see if chronic intercurrent therapy with β-adrenoceptor blocking drugs or calcium channel entry blockade reduced the incidence of postoperative SMI.

Patients and methods

After obtaining approval from the Local Ethics Committee and informed consent, 455 patients undergoing urological (n=93), orthopaedic (n=144), vascular or general abdominal surgery (n=218) underwent ambulatory ECG monitoring using Kontron Micro KI 5100 solid state digital recorders before operation and for the first 2 days after operation. All patients receiving chronic intercurrent medication (⩾1 month duration) continued this up to and including the morning of surgery, and recommenced as soon as feasible after the end of operation. β-Adrenoceptor blocking drugs used were mainly atenolol, but some patients were receiving oxprenolol, bisoprolol, propranolol, metoprolol, labetolol and sotalol. Similarly, most patients on chronic calcium channel entry blockade were receiving nifedipine, although some were receiving amlodipine, diltiazem, verapamil or felodipine.

Data from the ECG recorder were analysed using a computer program designed for analysis of ST-segment changes (Medilog Prima ECG Analysis System). A significant episode of ST-segment change was defined as horizontal or downsloping ST-segment depression of 1 mm or more, or ST-segment elevation of 2 mm or more lasting for 60 s or longer and followed by return to baseline for at least 1 min. Baseline was measured at a point 60 ms before the maximum R wave and the ST-segment was measured at a point 100 ms after the maximum R wave. All recorded episodes of ST-segment change were verified visually by one of the investigators.

The choice of premedication, anaesthetic technique, postoperative analgesia, intensity of intraoperative monitoring and postoperative oxygen therapy were at the discretion of the anaesthetist and according to the surgery undertaken. All cardiovascular drugs were recommenced by the morning after surgery unless the patient had a heart rate <50 beat min^{-1} or a systolic arterial pressure <100 mm Hg.

Patients were excluded from the study if their preoperative ECG revealed: evidence of left ventricular hypertrophy and strain changes in the lateral chest leads; conduction defects; changes caused by digoxin medication; or if there was inadequate data recording (<8 h) on any day in the pre- or postoperative period.

Statistical analysis

The primary end-point of the study was the occurrence of postoperative SMI and its association with β-adrenoceptor blockade or calcium channel entry blockade. Odds ratios were derived for the association between postoperative SMI and treatment. The statistical significance of these univariate associations was examined using chi-square tests for categorical data. The association between postoperative SMI and other patient characteristics and cardiovascular variables (sex, age >70 yr, history of smoking, vascular surgery, history of myocardial infarction or angina pectoris, history of arterial hypertension based on a general practitioner diagnosis and institution of appropriate medication, diabetes mellitus, preoperative SMI) was examined in the same way. A probability of less than 5% was accepted as statistically significant.

Data were analysed using logistic regression analysis (using Stata version 6.0 on a Viglen Pentium III 233 MHz microprocessor), where the terms for chronic intercurrent β-adrenoceptor blockade or calcium channel entry blockade were retained as the terms of interest. The influence of potential confounders was examined and retained in the final model if they had a clinically significant impact on the coefficients for β-adrenoceptor blockade and calcium channel entry blockade. Statistical significance was determined using a log-likelihood ratio test and the Wald test, and a probability of less than 5% was taken as significant.

The power of the study was calculated using the frequencies of postoperative SMI reported by Wallace and colleagues.[10] We determined that groups of 79 patients receiving β-adrenoceptor blockade and 374 unexposed controls would allow us to detect a difference in postoperative SMI at the 5% level with a power of 85%. A similar calculation based on the *post hoc* numbers of patients with postoperative SMI in the exposed calcium channel entry blockade and unexposed control groups indicated that the study had 65% power to detect a difference at the 5% significance level.

Results

Anaesthesia and surgery were uneventful in 454 patients; there was one intraoperative death. Three patients died of acute myocardial infarction during the first 3 days after operation. In two of these there were postoperative aECG data, and therefore these patients were included in the analysis. In the third, aECG data were available for the preoperative but not for the postoperative period, and this patient and the intraoperative death were excluded from further analysis. Therefore, we analysed data from 453 patients, of whom 308 (68%) were male and 45% were aged more than 70 yr.

Two hundred and fifty-one of 453 patients had coronary artery disease (previous myocardial infarct, typical angina or atypical angina with a positive stress test) or two or more risk factors for coronary artery disease (age >70 yr, hypertension, current smoker, hypercholesterolaemia, diabetes mellitus); 210 (46.4%) patients were receiving treatment for hypertension and 74 (16.3%) for ischaemic heart disease.

Seventy-nine (17.4%) patients were receiving chronic intercurrent β-adrenoceptor blockade for ischaemic heart disease or arterial hypertension on admission to hospital, and

Table 1 Age, indications for therapy and patients receiving other therapies in the different patient groups (number of patients in each subgroup) HT=Hypertension, Isch HD=ischaemic heart disease, ACEI=angiotensin converting enzyme inhibitors

		Indications for therapy				**Patients receiving**	
	Age (yr)	**HT**	**Isch HD**	**Both**	**Other**	**ACEI**	**Nitrates**
β-Adrenoceptor blockers	45–88	50	3	5	2	6	3
Calcium channel entry blockers	49–84	30	8	11	0	6	7
Combined blockade	55–78	12	1	6	0	3	2
Neither	40–97	–	–	–	–	34	6

Table 2 Cross-tabulation for univariate analysis of categorical risk factors and postoperative silent myocardial ischaemia (SMI) in 453 patients 1=Yes, 0=no, except in the case of sex, where 1=male and 0=female β-Block=β-Adrenoceptor blockade; CEB=calcium channel entry blockade Pre-SMI and post-SMI=pre- and postoperative silent myocardial ischaemia

	Patients coded 1		**Patients coded 0**			
	No. with post-SMI	**No. with no post-SMI**	**No. with post-SMI**	**No. with no post-SMI**	**Odds ratio (95% CI)**	***P***
Pre-SMI	53	13	78	309	16.15 (7.68–33.94)	0.001
β-Block	22	57	109	265	0.94 (0.54–1.65)	0.938
CEB	29	41	102	281	1.95 (1.15–3.32)	0.015
Hypertension	71	139	60	183	1.56 (1.03–2.35)	0.033
Vascular surgery	54	86	77	236	1.92 (1.25–2.96)	0.003
Myocardial infarction	20	38	111	284	1.35 (0.75–2.42)	0.317
Male sex	87	221	44	101	0.90 (0.59–1.39)	0.646
Smoking	23	64	108	258	0.80 (0.49–1.47)	0.601
Angina	12	22	119	300	1.38 (0.66–2.87)	0.394
Diabetes mellitus	6	28	125	294	0.50 (0.20–1.25)	0.132
Age >70 yr	66	138	65	184	1.35 (0.90–2.04)	0.145

70 (15.5 %) were receiving calcium channel entry blocking drugs. Twenty patients were receiving both β-blockade and calcium channel entry blocking medications. Seventy-eight percent of patients were receiving β-adrenoceptor blocking drugs for hypertension, 5% for coronary artery disease and 12% for both; similarly, 63% of patients taking calcium channel entry blocking drugs were receiving treatment for hypertension, 13% for coronary artery disease and 24% for both. Fifty-nine of 79 patients receiving β-adrenoceptor blocking drugs were receiving atenolol; others were receiving oxprenolol (one), bisoprolol (three), propranolol (six), metoprolol (five), labetolol (one) and sotalol (four). Fifty-three of 70 patients receiving calcium channel entry blocking drugs were receiving nifedipine; others received amilodipine (six), diltiazem (six), verapamil (four) or felodipine (one). The age ranges of the patient groups and indications for treatment, and other relevant cardiovascularly active therapies are shown in Table 1.

The association between the different variables and postoperative SMI, as examined by univariate analysis, is shown in Table 2. There was a significant association with four variables: preoperative SMI, vascular surgery, arterial hypertension and intercurrent treatment with calcium channel entry blocking drugs. There was no effect of β-adrenoceptor blockade on postoperative SMI (*P*=0.892). In 19 patients receiving both β-adrenoceptor and calcium channel entry blockers, 9 had no ECG changes associated with a perioperative SMI; four had postoperative SMI and six had both pre- and postoperative SMI.

The data were then submitted to logistic regression analysis. We examined for: the effects of confounding variables, as determined in Table 2; their effect on the coefficients of the odds ratio of the association for β-adrenoceptor blockade and calcium channel entry blockade; and postoperative SMI. We also examined for any potential interaction between β-adrenoceptor blockade and calcium channel entry blockade, and indications for the prescribing of these two drugs. However, there was no significant interaction between β-adrenoceptor blockade and calcium channel entry blockade for the occurrence of postoperative SMI (odds ratio 2.48 (95% confidence intervals 0.71–8.73)).

The final coefficients for the best fit model are shown in Table 3. There was no effect of diabetes mellitus, sex, history of smoking, angina or past myocardial infarction, or age greater than 70 yr. There were significant associations between calcium channel entry blockade and hypertension (odds ratio 9.32 (4.51–19.77)), calcium channel entry blockade and coronary artery disease (angina or a past history of myocardial infarction) (5.01 (2.71–9.02)), and β-adrenoceptor blockade and hypertension (21.05 (9.07–50.67)).

Discussion

In this re-analysis of observational data from four reported studies where the end-point was postoperative SMI, we found no effect of chronic intercurrent β-adrenoceptor blockade on the incidence of SMI, but noted an increased incidence of SMI in patients receiving chronic calcium channel entry blockade for either arterial hypertension or

Table 3 Logistic regression models for interaction of risk factors for occurrence of postoperative SMI after anaesthesia and surgery. *Comparison of likelihoods; 1df

			Log likelihood ratio test *vs* preceding model	
	Odds ratio (95% CI)	***P***	**Chi-square***	***P***
β-Adrenoceptor blockade	0.76 (0.44–1.35)	0.341		
Calcium channel entry blockade	2.24 (1.31–3.83)	0.003		
β-Adrenoceptor blockade	0.64 (0.35–1.15)	0.137	2.94	0.0866
Calcium channel entry blockade	1.90 (1.08–3.35)	0.026		
Hypertension	1.50 (0.94–2.40)	0.086		
β-Adrenoceptor blockade	0.67 (0.37–1.21)	0.180	5.41	0.0201
Calcium channel entry blockade	1.77 (1.00–3.13)	0.050		
Hypertension	1.38 (0.86–2.22)	0.177		
Vascular surgery	1.69 (1.09–2.63)	0.019		

coronary artery disease. We chose to analyse our data in the same manner as Mangano and colleagues, that is by comparing exposed patients (those receiving a particular drug therapy) against unexposed patients (those not receiving that particular drug). Interactions between drugs and their effects on postoperative SMI were determined by logistic regression analysis.

We have reported previously the effects of both a single oral premedicant dose of a β-adrenoceptor blocking drug in mild untreated hypertensive patients and chronic intercurrent β-adrenoceptor blockade with atenolol in treated hypertensive patients undergoing non-cardiac surgery under general anaesthesia.[7 8] There was a reduction in the incidence of observed ECG changes associated with myocardial ischaemia from 28% to 2%. Furthermore, the studies of Mangano and colleagues and Wallace and colleagues also showed a reduction in perioperative SMI and mortality over the first 2 yr after surgery.[9 10]

In our patients undergoing non-cardiac surgical procedures under general anaesthesia, those maintained on chronic intercurrent β-adrenoceptor blocking therapy did not show a reduction in the incidence of postoperative SMI. Why should our results be at variance with those of Stone and colleagues[7 8] and Wallace and colleagues?[10]

Compared with Stone and colleagues,[7] where untreated patients with mild hypertension (diastolic pressure <100 mm Hg) received a single dose of a β-adrenoceptor blocking drug with their premedication, patients in this meta-analysis continued to receive their normal β-adrenoceptor antagonist medication. Thus patients in our earlier study were different from the present group of patients, being mild-to-moderate untreated hypertensive patients (diastolic arterial pressure <100 mm Hg, with no ECG evidence of either left ventricular hypertrophy or myocardial ischaemia) compared with patients with arterial hypertension or ischaemic heart disease, or both. Chronic β-adrenoceptor treatment has been coupled with an increase in plasma high-density lipoproteins, which may itself increase the incidence of latent ischaemic heart disease.

In the second study by Stone and colleagues,[8] we compared patients maintained on β-adrenoceptor blocking drugs with untreated controls, and showed a peroperative incidence of ECG changes compatible with myocardial ischaemia of 0% (none of 14) *vs* 28% (11 of 39). However, this was a small study, and no patient had symptoms or clinical evidence of ischaemic heart disease.

There were also differences between our patients and those reported by Wallace and colleagues.[10] We did not confine our study to patients with ischaemic heart disease or to those with two or more risk factors, but chose to examine a general non-cardiac surgical population. Thus the incidence of patients with either coronary arterial disease or 'at-risk' of coronary disease was 55.4% in our study compared with 100% in the studies of Mangano and colleagues[9] and Wallace and colleagues.[10] There was also a significantly higher incidence of hypertension in association with diabetes mellitus in the American series. There may be differences in the incidence and types of other preoperative drug therapies and in compliance with their administration, in addition to differences in the duration and conduct of anaesthesia and surgery. Of additional concern is the fact that some patients in the Wallace study were receiving chronic β-adrenoceptor blockade which was stopped abruptly at the time of randomization–this may lead to the development of withdrawal features.[12] However, subsequent correspondence would suggest there were equal numbers of patients where β-adrenoceptor blockade was withdrawn before operation in both treatment arms.

Diabetes mellitus is a powerful risk factor for atherosclerosis, especially if associated with arterial hypertension and abnormalities of lipid metabolism (the so-called syndrome X).[13] Mangano and colleagues found three univariate predictors that influenced cardiac death: atenolol, diabetes mellitus and early postoperative SMI on days 0–2.[9] Atenolol improved 2-yr survival in diabetic patients by approximately 75%; in the absence of β-adrenoceptor blockade, the relative odds ratio for adverse outcome from diabetes mellitus were increased four-fold. Moreover, with multivariate analysis, diabetes mellitus alone and not atenolol treatment was a predictor of cardiac outcome.

In a separate study, using multivariate logistic regression to define risk factors, Hollenberg and colleagues found diabetes mellitus to be a predictor of postoperative SMI.[14] Thus diabetes may be a more important contributor towards cardiac complications than atenolol is in preventing it. The incidence of diabetes mellitus in our patients was low (7.5%) compared with 31% in the study of Wallace and colleagues.[10] Hence any effect of β-adrenoceptor blockade in improving outcome by reducing the influence of diabetes mellitus might be expected to be small or insignificant.

However, our results are in keeping with those of Hollenberg and colleagues[14] who were unable to find any difference in the incidence of postoperative SMI between patients maintained on β-adrenoceptor blocking drugs and those not receiving them. Similarly, both Mangano and colleagues and Browner and colleagues failed to find any effect of β-adrenoceptor blocking drugs on postoperative complications and mortality in patients undergoing non-cardiac surgery.[15 16] As further support for a possible difference between the populations studied by us and Mangano and colleagues, there are mortality data from the two study populations. While Mangano found cardiac mortality at 2 yr to be reduced in the atenolol-treated population from 12.5% to 4.2%,[9] Howell and colleagues, using a case-control design interrogation of the Oxford Record Linkage Study, found no association between preoperative β-adrenoceptor antagonist therapy and cardiovascular death within 30 days of surgery.[17]

The increased association of ischaemia and treatment with chronic calcium channel entry blockade (although only having a power of 65% to detect a significant difference at the 5% level) has been paralleled in other studies. Psaty and colleagues found an association between short-acting calcium channel entry blocking drugs and an increased risk of myocardial infarction in hypertensive patients,[18] and Mangano and colleagues found a univariate association between calcium entry blocking drugs and adverse long-term outcome in non-cardiac surgical patients.[15] In the latter study, other significant correlates included presence of cardiac disease, peripheral vascular disease, postoperative SMI and preoperative medication with nitrates. However, multivariate regression analysis failed to support the significance of calcium entry blockade, although significant correlates included a history of typical angina and postoperative SMI. Similarly, no association was found in the studies of Braun and colleagues or Jick and colleagues.[19 20]

Thus although Mangano and colleagues showed a positive effect of atenolol on both mortality and morbidity in a selected male population with a high incidence of hypertension and diabetes mellitus, we cannot confirm their findings. Furthermore, we found a significant association between postoperative SMI and calcium channel entry blockade. The clinical significance of these findings clearly establishes the need for prospective studies of cardiovascular outcome in patients receiving long-term intercurrent therapy for hypertension or coronary artery disease, and the possible benefits of perioperative prophylactic administration of β-adrenoceptor blocking drugs.

Acknowledgement

This work was supported by the Wellcome Trust.

References

1 Muir AD, Reeder MK, Foex P, Ormerod OJM, Sear JW, Johnston C. Preoperative silent myocardial ischaemia: incidence and predictors in a general surgical population. *Br J Anaesth* 1991; **67**: 373–7

2 Allman KG, Muir A, Howell SJ, Hemming AE, Sear JW, Foex P. Resistant hypertension and preoperative silent myocardial ischaemia in surgical patients. *Br J Anaesth* 1994; **73**: 574–8

3 Windsor A, French GWG, Sear JW, Foex P, Millett SV, Howell SJ. Silent myocardial ischaemia in patients undergoing transurethral prostatectomy. A study to evaluate risk scoring and anaesthetic technique with outcome. *Anaesthesia* 1996; **51**: 728–32

4 Howell SJ, Hemming AE, Allman KG, Glover L, Sear JW, Foex P. Predictors of postoperative myocardial ischaemia: The role of intercurrent arterial hypertension and other cardiovascular risk factors. *Anaesthesia* 1997; **52**: 107–11

5 French GWG, Lam WH, Rashid Z, Sear JW, Foex P, Howell S. Perioperative silent myocardial ischaemia in patients undergoing lower limb joint replacement surgery: an indicator of postoperative morbidity or mortality? *Anaesthesia* 1999; **54**: 235–40

6 Coriat P. Reducing cardiovascular risk in patients undergoing non-cardiac surgery. *Curr Opin Anaesthesiol* 1998; **11**: 311–14

7 Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HH, Triner L. Myocardial ischemia in untreated hypertensive patients: Effect of a single small oral dose of a beta-adrenergic blocking agent. *Anesthesiology* 1988; **68**: 495–500

8 Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HH, Triner L. Risk of myocardial ischaemia during anaesthesia in treated and untreated hypertensive patients. *Br J Anaesth* 1988, **61**: 675–9

9 Mangano DT, Layug EL, Wallace A, Tateo I for the Multicenter Study of Perioperative Ischemia Research Group. Effect of atenolol on mortality and cardiovascular morbidity after non-cardiac surgery. *New Engl J Med* 1996: **335**; 1713–20

10 Wallace A, Layug B, Tateo I, *et al.* Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology* 1998; **88**: 7–17

11 Neill F, Sear JW, French G, Lam H, Foex P, Hooper RJL. Cardiac troponins I and T as predictors of early postoperative cardiac complications. *Br J Anaesth* 1999; **82** (Suppl. 1): 45

12 Frishman WH, Klein N, Strom J, *et al.* Comparative effects of abrupt withdrawal of propranolol and verapamil in angina pectoris. *Am J Cardiol* 1982; **50**: 1191–5

13 Williams B. Insulin resistance: the shape of things to come. *Lancet* 1994; **344**: 521–4

14 Hollenberg M, Mangano DT, Browner WS, *et al.* for the Study of Perioperative Ischemia Research Group. Predictors of postoperative myocardial ischemia in patients undergoing noncardiac surgery. *JAMA* 1992; **268**: 205–9

15 Mangano DT, Browner WS, Hollenberg M, Li J, Tateo I for the Study of Perioperative Ischemia Research Group. *JAMA* 1992; **268**: 233–9

16 Browner WS, Li J, Mangano DT for the Study of Perioperative Ischemia Research Group. *JAMA* 1992; **268**: 228–32

17 Howell SJ, Sear YM, Yeates D, Goldacre M, Sear JW, Foex P. β-blockers and perioperative cardiovascular risk. *Br J Anaesth* 1999; **82**: 458P

18 Psaty BM, Heckbert SR, Koepsell TD, *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274**: 620–5

19 Braun S, Boyko V, Behar S, *et al.* Calcium antagonists and mortality in patients with coronary artery disease: a cohort study of 11,575 patients. *J Am Coll Cardiol* 1996; **28**: 7–11

20 Jick H, Derby LE, Gurewich V, Vasilakis C. The risk of myocardial infarction associated with antihypertensive treatment in persons with uncomplicated essential hypertension. *Pharmacotherapy* 1996; **16**: 321–6

British Journal of Anaesthesia 84 (3): 316–22 (2000)

Effect of midazolam on transfer function between beat-to-beat arterial pressure and inter-beat interval length

H. Schächinger*, B. U. Müller, W. Strobel, J. Drewe and R. Ritz

Division of Intensive Care Medicine, Department of Internal Medicine, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland

**Corresponding author*

Arterial pressure (AP) and inter-beat interval (IBI) length are under autonomic nervous system control. The control mechanisms can be investigated by transfer function analysis. It is not known if this type of analysis may be helpful in monitoring depth of sedation. In an open-label, uncontrolled investigation, the effect of midazolam on the transfer function between AP and IBI, and on spectral indices of AP and heart rate (HR) variability (APV, HRV) were assessed in the absence and presence of the benzodiazepine antagonist flumazenil. We studied 11 healthy male volunteers. After an initial control period of 60 min, we studied three consecutive periods, each of 60 min duration, with progressively increasing concentrations of midazolam (0.02, 0.06, 0.14 mg kg^{-1} h^{-1}). A final 60-min period during administration of flumazenil 0.004 mg kg^{-1} h^{-1} and while the agonist was still present was also studied. To confirm midazolam-induced central nervous system effects, electroencephalography was performed and Ramsay sedation scores were determined. With increasing dose of midazolam, the high frequency (0.15–0.4 Hz) component of the transfer function between AP and IBI decreased progressively (mean 26.5 (SEM 3.7), 19.2 (2.9), 12.8 (1.7), 8.4 (1.6) ms mm Hg^{-1}). This effect was antagonized by flumazenil (21.5 (3.2) ms mm Hg^{-1}). Other indices (e.g. HRV, APV) did not reveal such a clear response to midazolam dose and flumazenil application. Thus in healthy male volunteers, the transfer function between AP and IBI in the parasympathetically dominated high frequency range varies according to benzodiazepine agonism and antagonism. This finding has potential implications for monitoring the effects of benzodiazepines.

Br J Anaesth 2000; **84**: 316–22

Keywords: arterial pressure; reflexes, baroreflex; heart; heart rate; hypnotics benzodiazepine, midazolam; monitoring, electroencephalography

Accepted for publication: September 27, 1999

Benzodiazepines are important hypnotic, sedative, amnesic and anxiolytic drugs.[1–3] In intensive care medicine the benzodiazepine agonist midazolam is used frequently in patients requiring ventilatory support. Although midazolam has a relatively short half-life in healthy volunteers (approximately 2–3 h), active midazolam metabolites may be of significance in patients suffering from multiple organ failure.[4] In such circumstances, patients are at increased risk of oversedation. Oversedation enhances the likelihood of future benzodiazepine withdrawal problems and favours autonomic nervous system dysfunction, resulting in hypotension, respiratory depression and disturbed bowel motility. In contrast, undersedation may cause ventilatory problems, subject patients to pain and discomfort, and may cause stress-related activation of the autonomic nervous system, with subsequent increases in arterial pressure (AP), heart rate (HR) and oxygen demand. In routine care, clinicians need to grade the sedative effects of drugs. For this purpose, several sedation scores, description of motor responses to standard nursing procedures and electroencephalogram (EEG) and autonomic nervous system variables have been proposed.

Autonomic indices have the advantage that they are independent of verbal report and other muscular responses and thus may be determined during neuromuscular block. Common autonomic nervous system indices, such as AP and HR, are easy to identify but are not specific to the impact of anaesthetic drugs on the autonomic nervous system. Spectral analysis of AP variability (APV) and HR variability (HRV), and in particular transfer function analysis between AP and inter-beat interval (IBI) length, may provide important additional information on autonomic nervous system control.[5 6] Transfer function analysis between AP and IBI not only allows the user to estimate the magnitude of IBI changes associated with AP variations, but also differentiates between slow (less than 0.15 Hz) and fast

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

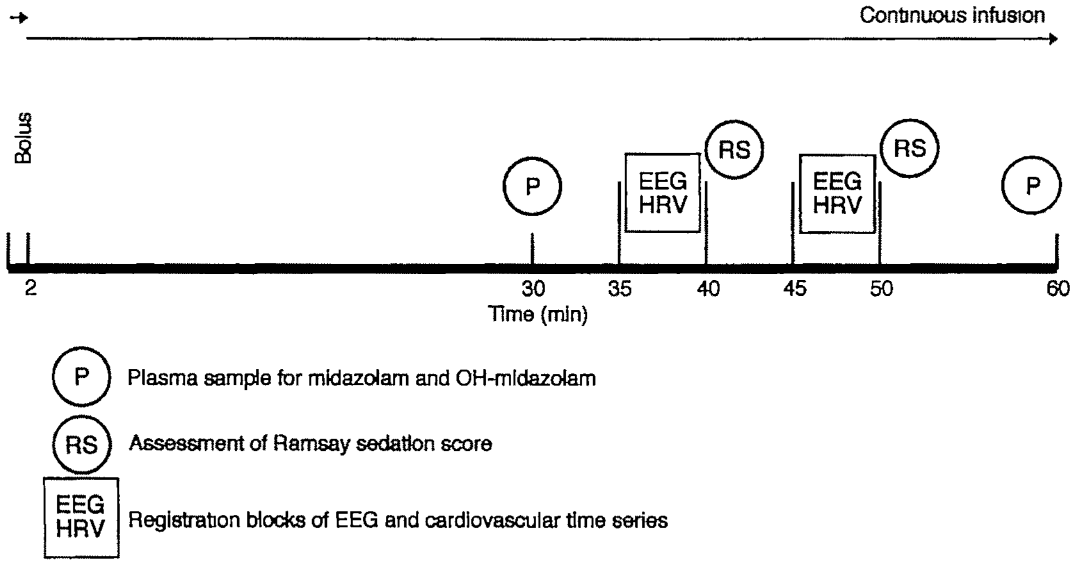

Continuous infusion
Bolus
P
EEG
HRV
RS
EEG
HRV
RS
P
2
30
35
40
45
50
60
Time (min)
P
Plasma sample for midazolam and OH-midazolam
RS
Assessment of Ramsay sedation score
EEG
HRV
Registration blocks of EEG and cardiovascular time series

Fig 1 Sequence of procedures during one infusion period

(greater than 0.15 Hz) components of this association.[5] However, the role of these techniques for monitoring the sedative effects of drugs needs to be investigated further. Thus, we performed a volunteer study to assess the effects of midazolam on APV, HRV and on transfer functions between AP and IBI using a simple dose regimen which also included administration of the benzodiazepine antagonist flumazenil. An electroencephalogram (EEG) was assessed simultaneously as a standard technique for monitoring sedative effects.

Subjects and methods

The study was performed according to the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee of the Department of Medicine, University Hospital of Basel.

We studied 11 male, healthy, non-smoking volunteers (aged 23–42 yr). All volunteers had a normal physical examination, and electrocardiography, routine blood chemistry and haematology and urine analysis were normal, with no evidence or history of illicit drug abuse or use of sedatives. Participants signed an informed consent before participating in the study.

Subjects entered the hospital at 08:00 after a light breakfast without caffeine-containing beverages. The study took place in the intensive care unit ward to guarantee optimal monitoring. Two peripheral venous lines were inserted into antecubital veins. Subjects were in supine position throughout the experiment. The sequence of interventions is illustrated in Figure 1.

Five successive periods were studied (see Fig. 1). The first was a 60-min control period. During the second experimental period, midazolam 0.02 mg kg^{-1} was administered i.v., half of the dose as a bolus (0.01 mg kg^{-1} over 2 min) followed by continuous infusion of the remainder (0.01 mg kg^{-1} over the remaining 58 min). During the third and fourth experimental periods, midazolam 0.06 and 0.14 mg kg^{-1} were given by bolus and infusion as above. The total dose of midazolam for a subject with a body weight of 70 kg was 15.4 mg. During the fifth experimental period, midazolam infusion was stopped and the benzodiazepine antagonist flumazenil was given i.v. (0.002 mg kg^{-1} as a bolus followed by 0.002 mg kg^{-1} as a constant infusion over the remaining hour) while the agonist was still present.

Plasma samples were obtained 30 min after the start of each period and at the end of each period (60 min). Samples were centrifuged and stored at –20°C for HPLC analyses of midazolam[7] with a detection limit of 1 ng ml^{-1}. During the flumazenil period, the 60-min sample was omitted. Averages of 30- and 60-min plasma midazolam concentrations were calculated.

Monitoring of cardiovascular data

During each infusion period, two 5-min blocks of cardiovascular and ECG data were recorded simultaneously. Non-invasive arterial finger AP was assessed continuously using the Finapres system.[8] Beat-to-beat systolic and diastolic AP were determined offline from the Finapres analogue output. Single-lead electrocardiogram was stored on personal computer (PC) by analogue to digital (AD) conversion (1 kHz per channel) for offline determination of IBI length. Ventilatory frequency was assessed by inductive plethysmography. Pulse oximetry was monitored continuously and standard cuff AP intermittently (Dinamap, Criticon, Florida, USA) for safety reasons.

Beat-to-beat analysis

APV was calculated by fast Fourier transform (FFT) after equidistant representation of systolic AP data.[9] HRV was determined by low-pass filtering of the event series (LPFES method), as suggested by Rompelman, Snijders and van Spronsen.[10] APV and HRV were analysed for each of the following frequency bands: total band (0.02–0.5 Hz), high band (0.15–0.4 Hz), low band (0.07–0.14 Hz) and very low band (0.02–0.06 Hz). HRV was adjusted to mean HR (modulation index, MI) as suggested previously.[11] All variables were log-transformed to achieve normally distributed measures; HRV was expressed as ln MI^2 and APV as ln mm Hg^2.

Transfer function analysis of beat-to-beat changes in IBI length and systolic AP data was performed using ACTS software in accordance with previous publications.[6 12 13] The modulus gain function was calculated over the frequency range 0.02–0.5 Hz. The modulus gain function is expressed in ms mm Hg^{-1}. For further statistical analysis, this function was adjusted to the coherence function, as suggested previously.[6] For graphical illustration of the modulus gain function over the entire spectrum (0.02–0.5 Hz), it was not adjusted to the coherence function between systolic AP and IBI length. We calculated separately the low and high frequency components of the transfer function between systolic AP and IBI by integrating the modulus gain function over the low and high frequency bands, thus resulting in two variables (LF and HF components of the transfer function between systolic AP and IBI). All variables were first derived for each 5-min block and then averaged between both blocks.

EEG registration

At the same time as cardiovascular variables were assessed, EEG data were recorded from FP1-T3, T3-O1, FP2-T4, T4-O2 (according to the International 10–20 System) with the subject's eyes closed. Ground was placed at the central forehead. The skin was prepared to yield impedance values lower than 3 kW at each electrode site. A Moberg Neurotrac II Continuous EEG Monitor (frequency range 0.5–45 Hz) was used to display and store (AD conversion 12 bit, 128 Hz) EEG data in consecutive 2-s epochs. To minimize artefacts, a 50-Hz notch filter was used. Variables analysed by FFT for each epoch included absolute power in the following frequency bands: entire spectrum (1.0–30.0 Hz), α power (8.0–12.5 Hz), $\beta 1$ power (12.5–20.0 Hz), $\beta 2$ power (20.0–30.0 Hz), δ power (1.0–4.0 Hz) and θ power (4.0–8.0 Hz). Because of the skewed distribution of absolute power values, natural logarithmic transforms (ln) were calculated. In addition, power in each frequency band was calculated as percentage of total power for each 2-s epoch, respectively. Median values of all EEG variables were calculated for each of the 5-min blocks, respectively. Averages of the two blocks were then calculated to yield final values which were entered into the statistical analysis. Because of this procedure the power values presented may not necessarily add up to 100%.

Subjective sedation score

Subjects were rated by two physicians according to a scale proposed by Ramsay and colleagues.[14] The Ramsay sedation score is defined as follows: awake levels—(1) anxious and/or agitated; (2) co-operative, oriented, and tranquil; (3) responds to commands; asleep levels—(4) quiescent with brisk response to light glabelar tap or loud auditory stimulus; (5) sluggish response to light glabelar tap or loud auditory stimulus; and (6) no response. Scores of the two physicians were averaged.

Statistical analysis

All statistical calculations were performed using SAS software (release 6.12, SAS Institute Inc., Cary, NC, USA). Data are reported as mean (SEM). A repeated measures analysis of variance (SAS General Linear Model Procedure) was applied for multivariate testing of dose and drug effects. Averages of the Greenhouse–Geisser and Huynh–Feldt adjusted P values are reported.[15] Contrasts between the third midazolam infusion period and flumazenil period were constructed *a priori* (non-adjusted P values are reported in tables). All testing was two-tailed. $P<0.05$ was considered significant.

Results

Midazolam and flumazenil were well tolerated by all subjects. No adverse events occurred during infusion and pulse oximetry revealed no clinically significant desaturation. Plasma midazolam concentrations at 30 and 60 min for each period are shown in Table 1. Ramsay sedation scores increased with higher doses of midazolam (baseline, median 2 (range 1–2); midazolam infusion of 0.02 mg kg^{-1}, 3 (2–4); midazolam infusion of 0.06 mg kg^{-1}, 4 (4–5); midazolam infusion of 0.14 mg kg^{-1}, 5 (4–6)) and decreased during flumazenil infusion (3 (2–4)).

Power analysis of EEG data revealed decreasing α power, increasing δ power and increasing $\beta 1$ power. All of the above effects were reversible during infusion of flumazenil (Table 2).

AP, HR and respiratory frequency data are shown in Table 3. HR and respiratory frequency increased whereas AP remained unaffected during infusion of midazolam.

In general, there was an increase in HRV and APV (Table 4) during the first midazolam dose followed by a decrease during higher midazolam doses. Administration of flumazenil did not result in significant changes in HRV or APV. However, the fast component (0.15–0.4 Hz) of the transfer function between AP and IBI showed a very close dose–response association to midazolam and this index increased substantially after administration of flumazenil. This was not true for the low frequency component. Figure 2 illustrates the averaged transfer functions between AP and IBI with increasing dose of midazolam. There was substantial overlap of the low frequency component (0.07–0.14 Hz) of the transfer function at different midazolam doses. This was not the case for the high frequency component. Figure 3 indicates that infusion of flumazenil induced an increase in the fast component of the transfer function between AP

Table 1 Mean (SEM) plasma concentrations of midazolam (MDZ) and 1-α-hydroxy-midazolam (OH-MDZ) 30 and 60 min after the onset of midazolam and flumazenil (FLU) infusions. *Below the limit of detection, na=not applicable

Plasma concn	Time (min)	Baseline	MDZ (0.02 mg kg^{-1})	MDZ (0.06 mg kg^{-1})	MDZ (0.14 mg kg^{-1})	FLU (0.03 mg kg^{-1})
MDZ (ng ml^{-1})	30	*	12.8 (3.8)	36.8 (2.7)	94.4 (4.3)	62.9 (4.0)
	60	*	11.5 (2.5)	36.6 (1.9)	90.5 (4.8)	na
OH-MDZ (ng ml^{-1})	30	*	1.4 (0.4)	2.2 (0.4)	5.6 (0.7)	7.1 (0.8)
	60	*	0.7 (0.4)	2.7 (0.4)	6.5 (1.0)	na

Table 2 Mean (SEM) EEG variables (α 8–12.5 Hz, β1 12.5–20 Hz, β2 20–30 Hz, δ 1–4 Hz, q 4–8 Hz) during midazolam (MDZ) and flumazenil (FLU) infusions Relative α power decreased, β1 power and δ power increased progressively with higher midazolam doses, all of these effects were antagonized by flumazenil p1=Repeated measures ANOVA for baseline/midazolam effect; p2=linear contrast between highest level of midazolam infusion and flumazenil period

EEG variable	Baseline	MDZ (0.02 mg kg^{-1})	MDZ (0.06 mg kg^{-1})	MDZ (0.14 mg kg^{-1})	p1	FLU (0.03 mg kg^{-1})	p2
Log power (ln μV^2)							
α power	5.9 (0.4)	5.1 (0.3)	5.0 (0.2)	5.1 (0.2)	0.005	4.8 (0.4)	0.62
β1 power	4.1 (0.1)	4.5 (0.2)	4.7 (0.1)	5.2 (0.3)	0.0001	4.6 (0.2)	0.008
β2 power	3.7 (0.1)	3.4 (0.1)	3.2 (0.1)	3.6 (0.3)	0.05	3.9 (0.2)	0.21
δ power	5.5 (0.1)	6.4 (0.2)	7.6 (0.3)	7.4 (0.3)	0.0001	5.5 (0.1)	0.001
θ power	4.8 (0.2)	5.1 (0.2)	5.4 (0.2)	5.1 (0.1)	0.04	4.4 (0.2)	0.01
Total power	6.8 (0.2)	7.1 (0.1)	8.0 (0.2)	7.9 (0.2)	0.0006	6.6 (0.1)	0.001
Relative (%)							
α power	40.9 (6.2)	19.7 (6.2)	10.5 (5.3)	8.9 (3)	0.0001	25.4 (6.4)	0.01
β1 power	9.4 (1.3)	8.6 (1.0)	5.4 (0.8)	14.3 (5.8)	0.21	16.7 (2.5)	0.54
β2 power	6.7 (1.0)	3.6 (0.8)	1.7 (0.7)	3.4 (1.5)	0.008	8.9 (1.4)	0.008
δ power	32.9 (3.6)	53.1 (4.0)	72.6 (4.6)	65.5 (7.9)	0.0001	38.2 (4.0)	0.005
θ power	14.7 (1.5)	14.6 (1.1)	8.8 (0.6)	6.7 (0.6)	0.0002	11.8 (0.6)	0.0001

Table 3 Mean (SEM) heart rate increased with higher doses of midazolam (MDZ) and decreased during flumazenil (FLU) infusion. Arterial pressure and respiratory frequency did not change significantly p1=Repeated measures ANOVA for baseline/midazolam effect, p2=linear contrast between highest level of midazolam infusion and flumazenil period

	Baseline	MDZ (0.02 mg kg^{-1})	MDZ (0.06 mg kg^{-1})	MDZ (0.14 mg kg^{-1})	p1	FLU (0.03 mg kg^{-1})	p2
Heart rate (beat min^{-1})	59 (2.6)	62 (3.3)	67 (3.7)	72 (5)	0.01	63 (3.6)	0.002
Systolic arterial pressure (mm Hg)	119 (1.2)	120 (1.6)	117 (2.5)	118 (2.1)	0.48	119 (2.7)	0.23
Diastolic arterial pressure (mm Hg)	63 (2)	65 (2.4)	60 (2.6)	61 (1.6)	0.13	64 (3)	0.29
Respiratory frequency (Hz)	0.23 (0.01)	0.23 (0.01)	0.25 (0.01)	0.27 (0.02)	0.06	0.26 (0.01)	0.59

Table 4 Mean (SEM) heart rate variability, arterial pressure variability and transfer function magnitude between arterial pressure and inter-beat-interval (IBI) length in different frequency bands during midazolam (MDZ) and flumazenil (FLU) infusions Frequency bands are defined as VLF=very low frequency, LF=low frequency, HF=high frequency. Transfer magnitude in the HF range decreased progressively with higher midazolam doses and this effect was antagonized by flumazenil. p1=Repeated measures ANOVA for baseline/midazolam effect; p2=linear contrast between highest level of midazolam infusion and flumazenil period

	Baseline	MDZ (0.02 mg kg^{-1})	MDZ (0.06 mg kg^{-1})	MDZ (0.14 mg kg^{-1})	p1	FLU (0.03 mg kg^{-1})	p2
Heart rate variability, log-transformed (ln MI^2)							
Total band (0.01–0.5 Hz)	8.2 (0.3)	8.9 (0.2)	8.1 (0.2)	8.0 (0.3)	0.06	8.5 (0.4)	0.35
VLF (0.02–0.06 Hz)	6.7 (0.2)	7.6 (0.2)	6.6 (0.2)	6.9 (0.4)	0.05	7.4 (0.3)	0.45
LF (0.07–0.14 Hz)	6.9 (0.3)	7.4 (0.2)	6.4 (0.2)	6.3 (0.5)	0.03	7.1 (0.3)	0.17
HF (0.15–0.4 Hz)	7.3 (0.4)	7.6 (0.4)	7.2 (0.3)	6.4 (0.5)	0.18	7.1 (0.5)	0.21
Arterial pressure variability, log-transformed (ln mm Hg^2)							
VLF (0.02–0.06 Hz)	2.5 (0.2)	3.3 (0.2)	2.7 (0.4)	2.7 (0.4)	0.11	2.4 (0.2)	0.43
LF (0.07–0.14 Hz)	1.5 (0.2)	2.0 (0.2)	1.4 (0.3)	1.5 (0.4)	0.02	1.5 (0.2)	0.82
Transfer function between arterial pressure and IBI (ms mm Hg^{-1})							
LF (0.07–0.14 Hz)	15.4 (2.2)	14.1 (2.4)	9.2 (1.3)	8.5 (1.4)	0.03	14.0 (3.2)	0.22
HF (0.15–0.4 Hz)	26.5 (3.7)	19.2 (2.9)	12.8 (1.7)	8.4 (1.6)	0.0003	21.5 (3.2)	0.002

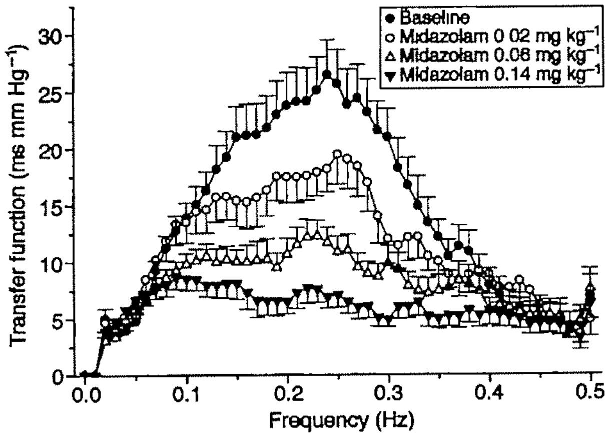


Fig 2 Transfer function between systolic arterial pressure (AP) and inter-beat interval (IBI) length during baseline and drug infusion. The high frequency component (0.15–0.4 Hz) of the transfer function between AP and IBI decreased according to the midazolam infusion dose. Substantial overlapping of the low frequency component (0.07–0 14 Hz) is evident. Data are mean (SEM)

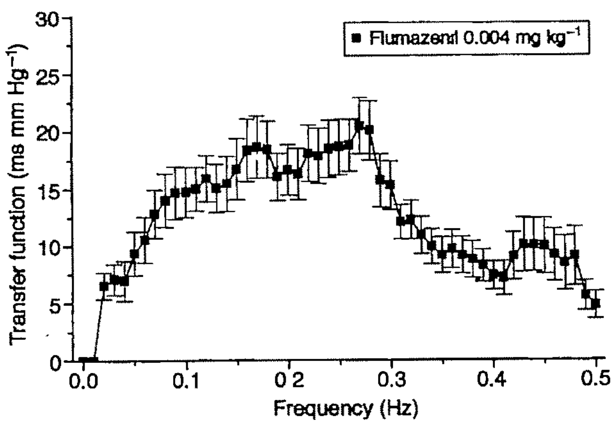


Fig 3 Increasing magnitude of the transfer function between systolic arterial pressure and inter-beat interval length during infusion of flumazenil. Data are mean (SEM).

and IBI. This fast component represented the only variable which decreased progressively with increasing dose of midazolam and increased again after administration of flumazenil in each subject (for individual changes see Fig. 4).

Discussion

Our main finding was that the high frequency component (0.15–0.40 Hz) but not the low frequency component (0.07–0.14 Hz) of the transfer function between systolic AP and IBI revealed a close relationship to midazolam dose, plasma concentration and antagonism with flumazenil.

High and low frequency components of the transfer function between AP and IBI are influenced by baroreflex HR control.[5 16 17] Indeed, transfer function analysis may be used to estimate baroreflex sensitivity.[6 12 18–23] Frequently, the magnitudes of the high and low frequency components have been averaged[18 19] to yield a single variable. However, baroreflex efferents are divided into two pathways: the fast parasympathetic branch to the sinus node and to other cardiac regions via the vagus nerve and the sympathetic branch, which is characterized by a slower signal transduction to cardiac and vascular effector cells. High frequency components (greater than 0.15 Hz) of AP and HR variations, therefore, cannot be of sympathetic origin. Modern signal analysis techniques, such as the transfer function analysis of beat-to-beat AP and HR data which were used in our investigation, make it possible to estimate the magnitude of the transfer function between AP and HR data separately in the vagally dominated high frequency range and in the low frequency range (which is believed to be of mixed sympathetic and parasympathetic origin).[24] We believe that this differentiation is of major importance as previous studies in animals have indicated an effect of benzodiazepines only on the vagal component of baroreflex HR control[25–29] whereas the sympathetic component remained unaffected. Our results are in accordance with animal data during pentobarbital anaesthesia when cross-spectral analysis of AP and HR revealed a gradual and dose-related decrease in the magnitude of the transfer function between AP and HR and baroreflex sensitivity.[30]

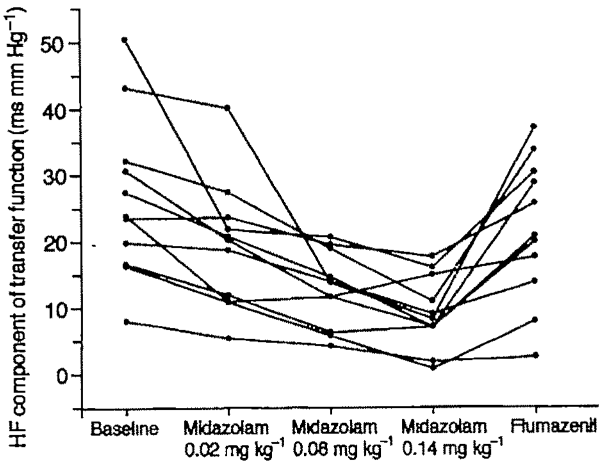


Fig 4 Individual data revealing progressive decrements of the high frequency (HF) component of the transfer function between systolic arterial pressure and inter-beat interval length in all subjects (only one subject showed an increase in the last midazolam infusion period) during midazolam infusion, and increments during flumazenil infusion.

Flumazenil antagonized the effects of midazolam on the fast component of the transfer function between AP and HR data. Flumazenil was given in the presence of midazolam. We cannot speculate about the intrinsic effects of flumazenil on baroreflex function and the transfer function between AP and HR data. One might expect increased baroreflex HR control, but data from animal studies indicated decreased baroreflex sensitivity after administration of benzodiazepine partial inverse agonists.[31] Thus this issue remains to be studied.

Traditional determination of baroreflex sensitivity in humans does not distinguish between sympathetic and parasympathetic effects of HR control.[32] Using standard techniques, it was shown that the sedative effects of benzodiazepines were accompanied by attenuated baroreflex HR control,[33] which is opposite to the effects of normal sleep.[34]

Several studies have addressed HRV during anaesthesia.[35] In our well controlled investigation of healthy volunteers, we found decreased HRV during higher midazolam doses, as was suggested by previous work.[36 37]

Using standard EEG techniques, we replicated the benzodiazepine-induced EEG changes and flumazenil effects described by others. This was true for the spectral EEG measures δ power, β power and α power.[38] However, several disadvantages limit the use of EEG techniques in routine clinical practice. The raw EEG signal is delicate, complex and needs to be judged correctly by trained staff. Furthermore, several procedures have been proposed to distinguish EEG changes during sedation (i.e. subjective judgement methods of the raw EEG signals; quantitative methods such as Fourier transformation; aperiodic analysis of EEG waveforms).[39] Complex, non-linear effects of benzodiazepines on the EEG have been described[39] thus making interpretation of EEG measures even more difficult.

It is promising that assessment of the transfer function between AP and IBI is not limited by such disadvantages. There would be no need for additional equipment other than that already used for cardiovascular monitoring, such as electrocardiography and continuous AP monitoring. Assessment does not depend on behavioural activity or verbal report, and may be obtained during neuromuscular block. A single variable can be derived. A disadvantage of the method is that it is applicable only in the presence of a sinus rhythm.

In summary, our investigation in healthy young volunteers revealed a close association between midazolam dose and spectral assessment of the fast component of the transfer function between AP and IBI. We suggest the use of frequency domain-based transfer function analysis for monitoring of the effects of midazolam in further patient studies. It is necessary to confirm these findings in real clinical settings.

References

1 Hobbs WR, Rall TW, Verdoorn TA. Hypnotics and sedatives; Ethanol. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 9th Edn. New York: McGraw-Hill, 1996; 361–96

2 Burns AM, Shelly MP, Park GR. The use of sedative agents in critically ill patients. *Drugs* 1992; **43**: 507–15

3 Ritz R. Benzodiazepine sedation in adult ICU patients. *Intensive Care Med* 1991; **17** (Suppl. 1): 11–14

4 Bauer TM, Ritz R, Haberthur C, *et al.* Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; **346**: 145–7

5 Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insight into cardiovascular regulation. *Am J Physiol* 1991; **261**: H1231–45

6 Robbe HWJ, Mulder LJM, Rüddel H, Langewitz W, Veldman JBP, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. *Hypertension* 1987; **10**: 538–43

7 Ha HR, Rentsch KM, Kneer J, Vonderschmitt DJ. Determination of midazolam and its alpha-hydroxy metabolite in human plasma and urine by high-performance liquid chromatography. *Ther Drug Monit* 1993; **15**: 338–43

8 Parati G, Casadei R, Groppelli A, Di Rienzo M. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. *Hypertension* 1989; **13**: 647–55

9 Mulder LJM, van Dellen HJ, van der Meulen P, Opheikens B. A spectral analysis program for cardiovascular time series. In: Maarse FJ, Mulder LJM, Sjouw W, Akkerman A, eds. *Computers in Psychology: Methods, Instrumentation and Psychodiagnostics.* Amsterdam: Swets and Zeitlinger, 1988; 30–38

10 Rompelman O, Snijders JB, van Spronsen CJ. The measurement of heart rate variability spectra with the help of a personal computer. *IEEE Trans Biomed Eng* 1982; **29**: 503–10

11 van Dellen HJ, Aasman J, Mulder LJM, Mulder G. Time domain versus frequency domain measures of heart rate variability. In: Orlebeke JF, Mulder G, van Doornen LJP, eds. *Psychophysiology of Cardiovascular Control.* New York: Plenum Press, 1985; 233–48

12 Schächinger H, Langewitz W, Rüddel H, *et al.* Spectral measures of short-term blood pressure and heart rate variations: Methodological considerations. *Homeostasis* 1996; **37**: 97–105

13 Haberthur C, Schachinger H, Langewitz W, Ritz R. Effect of beta blockade with and without sympathomimetic activity (ISA) on sympathovagal balance and baroreflex sensitivity. *Clin Physiol* 1999; **19**: 143–52

14 Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone–alphadalone. *BMJ* 1974; **2**: 656–9

15 Stevens J. *Applied Multivariate Statistics for the Social Sciences*, 3rd Edn. New Jersey: Lawrence Erlbaum Associates, 1996

16 de Boer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. *Am J Physiol* 1987; **253**: H680–9

17 de Boer RW, Karemaker JM, Strackee J. Comparing spectra of a series of point events particularly for heart rate variability data. *IEEE Trans Biomed Eng* 1984; **31**: 384–7

18 Pitzalis MV, Mastropasqua F, Passantino A, *et al.* Comparison between noninvasive indices of baroreceptor sensitivity and the phenylephrine method in post-myocardial infarction patients. *Circulation* 1998; **97**: 1362–7

19 James MA, Panerai RB, Potter JF. Applicability of new techniques in the assessment of arterial baroreflex sensitivity in the elderly: a comparison with established pharmacological methods. *Clin Sci* 1998; **94**: 245–53

20 Watkins LL, Fainman C, Dimsdale J, Ziegler MG. Assessment of baroreflex control from beat-to-beat blood pressure and heart rate changes: a validation study. *Psychophysiology* 1995; **32**: 411–14

21 Watkins L, Grossman P, Sherwood A. Noninvasive assessment of baroreflex control in borderline hypertension. Comparison with the phenylephrine method. *Hypertension* 1996; **28**: 238–43

22 Maestri R, Pinna GD, Mortara A, La Rovere MT, Tavazzi L. Assessing baroreflex sensitivity in post-myocardial infarction patients: comparison of spectral and phenylephrine techniques. *J Am Coll Cardiol* 1998; **31**: 344–51

23 Lord SW, Clayton RH, Hall MC, *et al.* Reproducibility of three different methods of measuring baroreflex sensitivity in normal subjects. *Clin Sci* 1998; **95**: 575–81

24 Stauss HM, Anderson EA, Haynes WG, Kregel KC. Frequency response characteristic of sympathetically mediated vasomotor waves in humans. *Am J Physiol* 1998; **274**: H1277–83

25 Sakomoto M, Yasumoto, Oshumi H, Choi H, Shibata Y, Kano T. Effects of midazolam and flumazenil on carotid sinus baroreflex control of circulation in rabbits. *Br J Anaesth* 1994; **73**: 384–7

26 DiMicco JA. Evidence for control of vagal tone by benzodiazepine receptors. *Neuropharmacology* 1987; **26**: 553–9

27 DiMicco JA. Blockade of forebrain gamma-aminobutyric acid (GABA) receptors and reflex activation of the cardiac vagus in anesthetized cats *J Pharmacol Exp Ther* 1982; **223**: 654–61

28 Conahan ST, Vogel WH. The effect of diazepam administration on heart rate and mean arterial blood pressure in resting and stressed conscious rats. *Res Commun Chem Pathol Pharmacol* 1986; **53**: 301–17

29 Gerold M, Cavero I, Riggenbach H, Wall M, Haeusler G. Analysis of cardiac chronotropic responses to diazepam and bromazepam in conscious trained dogs. *Eur J Pharmacol* 1976; **35**: 361–8

30 Yang CC, Kuo TB, Chan SH. Auto- and cross-spectral analysis of cardiovascular fluctuations during pentobarbital anesthesia in the rat. *Am J Physiol* 1996; **270**: H575–82

31 Berntson GG, Hart S, Sarter M. The cardiovascular startle response: anxiety and the benzodiazepine receptor complex. *Psychophysiology* 1997; **34**: 348–57

32 Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. *Circ Res* 1969; **24**: 109–21

33 Marty J, Gauzit R, Lefevre P, *et al.* Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. *Anesth Analgesia* 1986; **65**: 113–19

34 Conway J, Boon N, Jones JV, Sleight P. Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypertension* 1983; **5**: 746–8

35 Pomfrett CJD, Barrie JR, Healy TEF. Respiratory sinus arrhythmia: an index of light anaesthesia. *Br J Anaesth* 1993; **71**: 212–17

36 Haberthur C, Lehmann F, Ritz R. Assessment of depth of midazolam sedation using objective parameters. *Intensive Care Med* 1996; **22**: 1385–90

37 Galletly DC, Williams TB, Robinson BJ. Periodic cardiovascular and ventilatory activity during midazolam sedation. *Br J Anaesth* 1996; **76**: 503–7

38 Feshchenko VA, Veselis RA, Reinsel RA. Comparison of the EEG effects of midazolam, thiopental, and propofol: The role of underlying oscillatory systems. *Neuropsychobiology* 1997; **35**: 211–20

39 Buhrer M, Maitre PO, Hung O, Stanski DR. Electroencephalographic effects of benzodiazepines: choosing an electroencephalographic parameter to measure the effect of midazolam on the central nervous system. *Clin Pharmacol Ther* 1990; **48**: 544–54

British Journal of Anaesthesia **84** (0) 323–9 (2000)

Biphasic changes in autonomic nervous activity during pregnancy

C.-D. Kuo[1 2*], G.-Y. Chen[2 3], M.-J. Yang[4], H.-M. Lo[3] and Y.-S. Tsai[5]

[1]Cardiopulmonary Laboratory, Respiratory Therapy Department and [4]Department of Obstetrics and Gynaecology, Veterans General Hospital-Taipei, Taipei, Taiwan, Republic of China. [2]Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, Republic of China. [3]Department of Medicine, Tao-Yuan General Hospital, Tao-Yuan, Taiwan, Republic of China. [5]Department of Biomedical Engineering, Chung-Yuan Christian University, Chung-Li, Taiwan, Republic of China

**Corresponding author: Cardiopulmonary Laboratory, Respiratory Therapy Department, Veterans General Hospital-Taipei, Taipei, Taiwan 112, Republic of China*

To understand the sequential response of the autonomic nervous system to pregnancy, we studied heart rate variability in 23 first trimester, 23 second trimester and 21 third trimester pregnant women. Twenty non-pregnant women were recruited as controls. Time and frequency domain measures of heart rate variability in three recumbent positions were compared. We found that normalized high-frequency power in the supine position increased significantly in the first trimester (42.2 (95% confidence interval (CI) 5.4) nu (normalized unit); $P<0.05$) compared with non-pregnant controls (33.0 (6.0) nu), and then decreased progressively in the second (27.3 (6.7) nu) and third (21.8 (6.0) nu; $P<0.05$) trimesters. The low-/high-frequency power ratio in the supine position decreased significantly in the first trimester (0.8 (0.3); $P<0.05$) compared with that of non-pregnant controls (1.1 (0.3)) and increased progressively in the second (1.5 (0.4)) and third (2.1 (0.8); $P<0.05$) trimesters. When the position was changed from the supine to the right lateral decubitus, the percentage change in normalized high-frequency power correlated significantly and negatively with normalized high-frequency power in the supine position in non-pregnant controls ($r=-0.56$, $P=0.01$) and in pregnant women in the first ($r=-0.44$, $P=0.034$), second ($r=-0.68$, $P<0.001$) and third ($r=-0.68$, $P<0.001$) trimesters. These results indicate that autonomic nervous activity shifted towards a lower sympathetic and higher vagal modulation in the first trimester, and changed towards a higher sympathetic and lower vagal modulation in the third trimester as gestational age increased. The balance between the haemodynamic changes of pregnancy and aortocaval compression caused by the enlarging gravid uterus may be responsible for the biphasic changes in autonomic nervous activity during pregnancy.

Br J Anaesth 2000; **84**: 323–9

Keywords: heart, heart rate; parasympathetic nervous system; sympathetic nervous system; cardiovascular system, effects; pregnancy

Accepted for publication: November 1, 1999

Pregnancy is associated with substantial changes in the cardiovascular system. It has been noted that blood volume, cardiac output and stroke volume begin to change after the first trimester to accommodate the growing fetus.[1 2] Systemic vascular resistance is also decreased in response to haemodynamic changes.[3–5] As pregnancy advances, aortocaval compression from the gravid uterus gradually becomes evident, which may cause supine hypotensive syndrome in late pregnancy.[6]

In previous reports, decreased heart rate variability has been demonstrated during pregnancy, but there was no consensus as to the changes in autonomic nervous activity.[7–11] Inadequate stratification of gestational stages might be the main cause of this discrepancy. In a previous study, we found that autonomic nervous activity was shifted to lower vagal and higher sympathetic modulation in late pregnancy.[12] Aortocaval compression was suggested to be the main factor responsible for this change. This theory was supported by observations that moving to an upright position could lead to lessening of sympathetic activation[13] and that delivery of the fetus led to return to normal autonomic nervous activity within 3 months.[14]

During the early stages of pregnancy, autonomic nervous activity may be expected to vary little from that of the non-pregnant woman because aortocaval compression is absent. However, haemodynamic studies during pregnancy suggest

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

that autonomic nervous activity in the early stages of pregnancy is in fact different from the pre-pregnant state. As the autonomic nervous system plays an important role in adaptation of the maternal body to nurturing the fetus, it is important to understand the sequential changes in the autonomic nervous activity at various stages of pregnancy. Therefore, in this study, we have investigated the sequential changes in autonomic nervous activity during the three trimesters of pregnancy and between pregnant women in different trimesters and non-pregnant women.

Subjects and methods

This study was approved by the Hospital Committee for Human Investigation and informed consent was obtained from each subject before electrocardiographic recording. All pregnant women had a singleton vertex fetus with no obstetric or medical complications. They were advised to report symptoms of cardiovascular distress during the study, especially if they were supine. All women presented for study at the same time of day (14:00–16:00 after a light lunch at noon) to avoid the effects of circadian rhythms on heart rate variability. Those who drank any alcohol, were smokers, had any medical illness or who were receiving any medication were excluded.

The procedure for electrocardiographic recording and heart rate variability analysis was similar to our previous study.[12] All subjects were instructed not to drink caffeinated beverages for at least 24 h before electrocardiographic recording. Three recumbent positions were assumed in random order by the subjects (supine, left lateral decubitus and right lateral decubitus). After 5 min rest in each position, a continuous analogue signal of lead II of the electrocardiogram was recorded over 15 min by the bedside electrocardiographic monitor (Model 90621A, Spacelabs Inc., Redmond, WA, USA) and transmitted to a personal computer for recording. If there was any sign or symptom of intolerance to the supine position such as restlessness, breathlessness, pallor, dizziness or faintness, the electrocardiographic recording was discontinued and the position of the pregnant woman was changed from supine to upright or lateral tilt.

As 2^m elements of data are needed by the fast Fourier transformation algorithm where m is an integer,[15] and as a short-term recording of several minutes is needed for analysis of both sympathetic and vagal nervous systems,[16] the last stationary 512 RR intervals were used for calculation of the power spectrum by fast Fourier transformation (Mathcad, Mathsoft Inc., Cambridge, MA, USA). The direct current component was excluded before calculation of the power spectra. The area under the spectral peaks within the frequency range 0.01–0.4 Hz was defined as total power, the area under the spectral peaks within the range 0.04–0.15 Hz as low-frequency power and the area under the spectral peaks within the range 0.15–0.4 Hz as high-frequency power. Normalized high-frequency power (high-frequency power/total power) was used as an index of vagal modulation, normalized low-frequency power (low-frequency power/total power) as an index of sympathetic and vagal modulation and the low-/high-frequency power ratio as an index of sympathovagal balance.[17–19] The mean, SD and coefficient of variation of the same 512 RR intervals were calculated using standard formulae.

To assess the effect on normalized high-frequency power of changing position from supine to lateral decubitus, we defined $nHFP_{R/S}$ and $nHFP_{L/S}$ according to the formulae:

$$nHFP_{R/S} = 100\% \times \frac{nHFP_R - nHFP_S}{nHFP_S}$$

$$nHFP_{L/S} = 100\% \times \frac{nHFP_L - nHFP_S}{nHFP_S}$$

where $nHFP_S$=normalized high-frequency power in the supine position; $nHFP_R$=normalized high-frequency power in the right lateral decubitus position; $nHFP_L$= normalized high-frequency power in the left lateral decubitus position; and $nHFP_{R/S}$ and $nHFP_{L/S}$= percentage changes in normalized high-frequency power when the position was changed from supine to right and left lateral decubitus positions, respectively. In the same manner, $nLFP_{R/S}$, $nLFP_{L/S}$, $LFP/HFP_{R/S}$ and $LFP/HFP_{L/S}$ were defined for assessment of the effect on normalized low-frequency power or low-/high-frequency power ratio of changing position from the supine to right or left lateral decubitus position.

Values of heart rate variability measures in both time and frequency domains are presented as mean (95% confidence interval (CI)). Analysis of variance on ranks (SigmaStat statistical software, Jandel Scientific, San Rafael, CA, USA) was used to compare measures of heart rate variability during different trimesters of pregnancy. Significant differences were analysed further by pairwise comparison using Dunn's test. A Mann–Whitney rank sum test or unpaired *t* test was used to compare measures of heart rate variability between pregnant women in different trimesters and non-pregnant women. Repeated measures analysis of variance on ranks was used to compare measures of heart rate variability in the three recumbent positions. The correlation between $nHFP_{R/S}$ (or $nHFP_{L/S}$) and $nHFP_S$ was assessed by linear regression analysis in non-pregnant controls and pregnant women in different trimesters. $P<0.05$ was considered statistically significant.

We assumed that the expected difference in mean normalized high-frequency power was 10 normalized units (nu) and the expected SD was 10 nu. Using an alpha level of 5%, a power of 80% and assuming 8% of subjects would be excluded from the final analysis because of intolerance caused by the supine hypotensive syndrome,[20] we calculated that a sample of 20 patients would be required.

Results

Twenty-three pregnant women in the first, 23 in the second and 23 in the third trimesters, and 20 healthy age-matched

Table 1 Heart rate variability measures of pregnant women in the three trimesters and in non-pregnant women (mean (95% CI)) nu=Normalized unit *$P<0.05$ compared with non-pregnant women, †$P<0.05$ compared with first trimester; ‡$P<0.05$ between different recumbent positions

	Non-pregnant	1st trimester	2nd trimester	3rd trimester
Subjects	20	23	23	21
Age (yr)	29.8 (1.6)	30.3 (1.9)	30.9 (1.9)	29.3 (1.9)
Gestational age (weeks)		11.0 (0.8)	21.3 (2.1)	36.5 (2.0)
Mean RR interval (ms)				
Supine	820.1 (34.2)‡	803.5 (38.7)‡	708.8 (31.4)*†‡	680.9 (34.6)*†‡
Right decubitus	821.8 (36.0)	808.8 (45.2)	715.7 (26.5)*†	691.5 (26.1)*†
Left decubitus	860.8 (44.5)	851.8 (49.1)	753.9 (28.3)*†	734.6 (28.1)*†
SD of RR intervals (ms)				
Supine	40.3 (6.0)	37.8 (5.7)‡	32.7 (5.2)	29.0 (5.3)*
Right decubitus	40.5 (5.7)	37.5 (7.1)	30.7 (4.4)*	27.4 (6.1)*
Left decubitus	40.9 (5.8)	41.5 (7.1)	32.2 (4.4)*	30.2 (5.1)*
Coefficient of variation of RR intervals (%)				
Supine	4.9 (0.7)	4.6 (0.6)	4.6 (0.8)	4.2 (0.7)
Right decubitus	4.9 (0.7)	4.5 (0.7)	4.3 (0.5)	3.9 (0.7)*
Left decubitus	4.7 (0.6)	4.8 (0.7)	4.3 (0.5)	4.1 (0.6)
Total power (ms^2)				
Supine	639.2 (180.3)	600.2 (214.6)‡	360.7 (140.7)*	253.9 (98.8)*†
Right decubitus	668.2 (195.9)	496.6 (199.1)*	357.0 (119.6)*	241.5 (78.3)*
Left decubitus	674.2 (209.0)	570.7 (221.8)	416.3 (132.2)*	325.0 (115.9)*
High-frequency power (ms^2)				
Supine	212.5 (72.8)	258.7 (100.2)	114.1 (65.9)*†‡	59.4 (30.9)*†‡
Right decubitus	298.8 (96.4)	339.5 (145.5)	141.6 (57.9)*	70.1 (30.3)*†
Left decubitus	343.0 (115.2)	366.4 (156.0)	152.7 (58.2)*	113.4 (55.2)*†
Low-frequency power (ms^2)				
Supine	190.0 (56.6)	149.8 (55.9)‡	99.6 (39.3)*	76.3 (31.1)*†‡
Right decubitus	181.3 (62.4)	134.5 (53.2)	92.5 (28.1)*	65.7 (21.9)*
Left decubitus	170.8 (80.8)	182.9 (65.0)	126.5 (48.1)	100.7 (41.7)*
Normalized high-frequency power (nu)				
Supine	33.0 (6.0)‡	42.2 (5.4)*	27.3 (6.7)†‡	21.8 (6.0)*†
Right decubitus	44.9 (6.9)	50.2 (6.4)	37.3 (6.2)†	26.8 (5.2)*†
Left decubitus	41.3 (9.6)	46.5 (6.6)	36.3 (5.6)	30.0 (6.2)*†
Normalized low-frequency power (nu)				
Supine	30.0 (3.8)	27.4 (5.1)‡	29.1 (4.0)	29.8 (2.7)
Right decubitus	26.3 (3.9)	22.4 (3.3)	27.0 (4.1)	28.4 (3.2)†
Left decubitus	27.2 (4.6)	25.8 (3.3)	31.1 (4.2)	31.8 (4.3)
Low-/high-frequency power ratio				
Supine	1.1 (0.3)‡	0.8 (0.3)*‡	1.5 (0.4)†‡	2.2 (0.8)*†
Right decubitus	0.7 (0.2)	0.5 (0.2)	0.9 (0.2)†	1.4 (0.5)*†
Left decubitus	1.0 (0.3)	0.7 (0.2)	1.1 (0.3)	1.4 (0.5)†

non-pregnant women were recruited to this cross-sectional study. Two pregnant women in the third trimester felt faint when they lay in the supine position. Therefore, 23 first trimester, 23 second trimester and 21 out of 23 third trimester pregnant women were included for data analysis. The age of the non-pregnant women and pregnant women did not differ significantly (Table 1).

Figure 1 shows representative power spectra of a non-pregnant woman and three pregnant women in the different trimesters of pregnancy in three recumbent positions. The power spectra of the pregnant women had a greater spectral density in the first trimester and a gradually decreased power spectral density in the second and third trimesters in all frequency ranges in the three recumbent positions. After normalization, the normalized high-frequency power in the first trimester was higher than that of non-pregnant controls, while the low-/high-frequency power ratio was lower than that of non-pregnant controls in the three recumbent positions. In the second and third trimesters, normalized high-frequency power decreased. The low-/high-frequency power ratio increased gradually as gestational age increased in the three recumbent positions.

Table 1 shows heart rate variability measures in the three recumbent positions in the non-pregnant women and in pregnant women in the three trimesters of pregnancy. In the time domain, mean RR interval in the three recumbent positions decreased progressively when gestational age increased. Mean RR interval in the second and third trimesters was significantly lower than that of non-pregnant controls in the three recumbent positions. The SD and coefficient of variation of the RR intervals in the three recumbent positions also decreased progressively as gestational age increased. The SD of the RR intervals in the second and third trimesters was significantly lower than that of non-pregnant controls in both lateral decubitus positions. The coefficient of variation of the RR intervals in the third trimester in the right lateral decubitus position was significantly lower than that of non-pregnant controls.

In the frequency domain, total power and low-frequency power of the pregnant women in the three recumbent

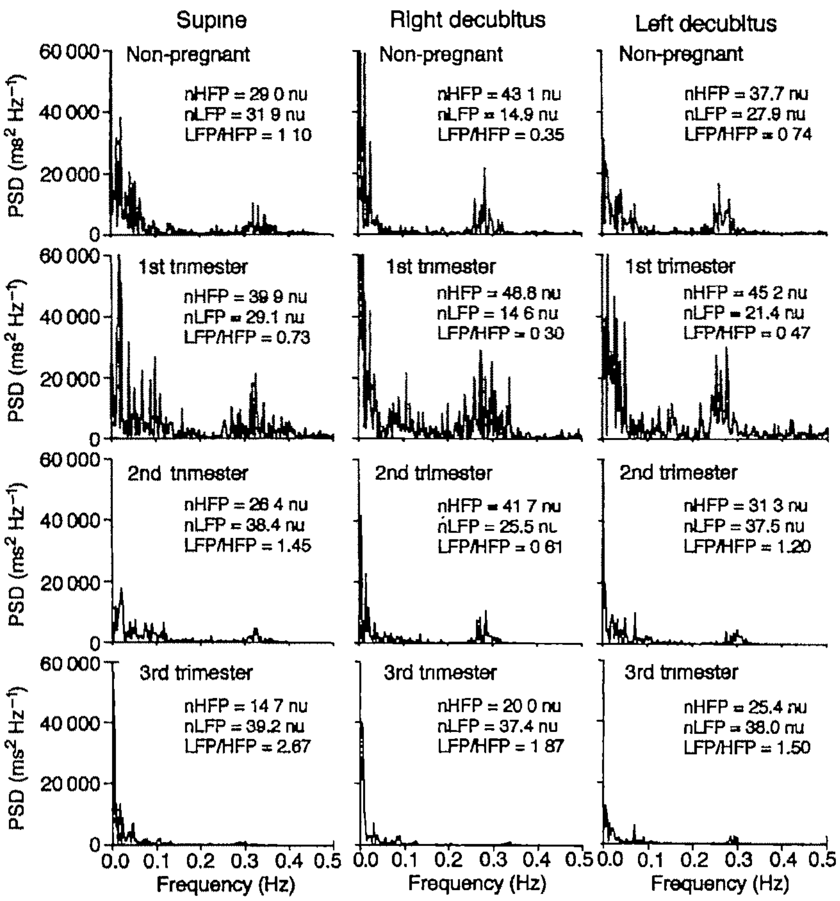


Fig 1 Representative heart rate power spectra in a non-pregnant woman and pregnant women in the three trimesters of pregnancy in three recumbent positions. Normalized high-frequency power (nHFP) was higher and the low-/high-frequency power ratio (LFP/HFP) was lower in the first trimester compared with the non-pregnant control in the three recumbent positions. As gestational age increased, nHFP became progressively lower and LFP/HFP progressively increased

positions decreased progressively as gestational age increased. Total power, high-frequency power and low-frequency power in the second and third trimesters were lower than those of non-pregnant controls in the three recumbent positions. The high-frequency power and normalized high-frequency power in the pregnant women increased in the first trimester compared with non-pregnant women, and then decreased progressively in the second and third trimesters. Similarly, normalized low-frequency power and the low-/high-frequency power ratio decreased in the first trimester compared with non-pregnant women, and then increased progressively in the second and third trimesters. In the supine position, normalized high-frequency power was significantly higher and low-/high-frequency power was significantly lower in the first trimester than in non-pregnant controls.

Table 2 shows the effect of position on autonomic nervous activity in pregnant women in different trimesters compared with non-pregnant women. The percentage change in normalized high-frequency power and the low-/high-frequency power ratio when the position was changed from the supine to the right or left lateral decubitus position in the first trimester was smaller than in non-pregnant controls.

When the position was changed from supine to right lateral decubitus, $nHFP_{R/S}$ correlated significantly and negatively with $nHFP_S$ in both non-pregnant controls and pregnant women in the three trimesters of pregnancy (left panel, Fig. 2). The slope of the regression between $nHFP_{R/S}$ and $nHFP_S$ decreased in the first trimester and then increased progressively in the second and third trimesters compared with non-pregnant women. When the position was changed from supine to left lateral decubitus, $nHFP_{L/S}$ correlated significantly and negatively with $nHFP_S$ in pregnant women in the second and third trimesters of pregnancy, and the slope in the third trimester was greater than that in the second trimester (right panel, Fig. 2).

Discussion

Although investigators have found decreased heart rate variability during pregnancy, there was no consensus as to changes in autonomic nervous activity as pregnancy progressed.[7–11] Vagal modulation was claimed to be increased, not changed or decreased, by different investigators compared with non-pregnant women.[7–11] Inadequate stratification of gestational stages and insufficient numbers

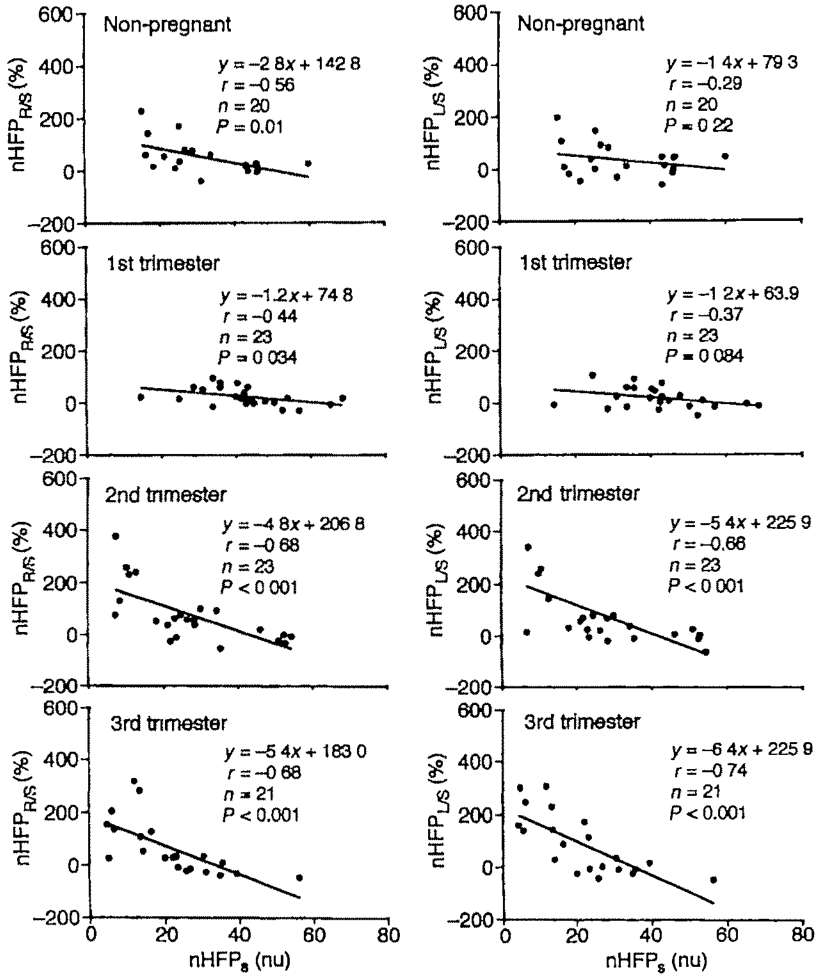


Fig 2 Linear regression between $nHFP_{R/S}$ (left panel, percentage change in normalized high-frequency power when the position was changed from supine to right lateral decubitus) or $nHFP_{L/S}$ (right panel, percentage change in normalized high-frequency power when the position was changed from supine to left lateral decubitus) and $nHFP_S$ (normalized high-frequency power in the supine position) in non-pregnant controls and pregnant women in the three trimesters.

Table 2 Percentage change in spectral heart rate variability measures in the three trimesters of pregnancy and in non-pregnant women when the position was changed from supine to lateral decubitus (mean (95% CI)) $nHFP_{R/S}$=percentage change in normalized high-frequency power when the position was changed from the supine to the right lateral decubitus; $nHFP_{L/S}$ =percentage change in normalized high-frequency power when the position was changed from the supine to the left lateral decubitus, $nLFP_{R/S}$ =percentage change in normalized low-frequency power when the position was changed from the supine to the right lateral decubitus, $nLFP_{L/S}$ =percentage change in normalized low-frequency power when the position was changed from the supine to the left lateral decubitus, $LFP/HFP_{R/S}$=percentage change in low-/high-frequency power ratio when the position was changed from the supine to the right lateral decubitus, $LFP/HFP_{L/S}$ = percentage change in low-/high-frequency power ratio when the position was changed from the supine to the left lateral decubitus

	. Non-pregnant	1st trimester	2nd trimester	3rd trimester
$nHFP_{R/S}$ (%)	49.5 (30.4)	23.5 (14.9)	76.4 (46.5)	64.4 (48.0)
$nHFP_{L/S}$ (%)	32.0 (30.0)	14.3 (17.3)	77.9 (55.1)	86.2 (52.3)
$nLFP_{R/S}$ (%)	−7.5 (16.4)	−13.0 (12.2)	1.5 (20.2)	−0.7 (15.4)
$nLFP_{L/S}$ (%)	−7.3 (13.7)	0.1 (10.9)	12.9 (15.9)	9.3 (16.6)
$LFP/HFP_{R/S}$ (%)	−22.5 (28.2)	−19.5 (19.9)	−23.6 (20.7)	−14.8 (25.2)
$LFP/HFP_{L/S}$ (%)	−3.5 (35.8)	1.7 (21.9)	−9.1 (26.1)	−13.9 (25.3)

of patients might be the causes of these discrepancies. The response of the autonomic nervous system to haemodynamic changes and aortocaval compression which occurs during pregnancy may vary with the different stages of pregnancy.[1-6] Thus, autonomic nervous activity should be studied separately in the different trimesters.

In this study, we demonstrated that autonomic nervous activity shifted to a higher vagal and lower sympathetic modulation in the first trimester of pregnancy in the three recumbent positions, especially in the supine position. Several factors may be responsible for these changes. First, blood volume increases substantially during pregnancy, starting as early as the sixth week of gestation and increasing rapidly until mid-pregnancy; thereafter it continues to increase but at a slower rate.[1] This augmentation of blood volume may increase cardiac output early in pregnancy. Changes in blood volume and haemodynamics may reduce the workload of the heart and consequently shift the autonomic nervous system into a state of lower sympathetic and higher vagal modulation. Second, systemic arterial pressure begins to decrease during the first trimester and reaches a nadir in mid-pregnancy.[2] The decline in systemic vascular resistance is probably caused by gestational hormones, increased concentrations of circulating prostaglandins, increased heat production by the developing fetus and development of a low-resistance circulation in the pregnant uterus.[2–4] The decline in systemic vascular resistance may reduce the workload of the heart, leading to lower sympathetic and higher vagal modulation in the first trimester of pregnancy. Third, aortocaval compression is still negligible at this stage. Although the supine hypotensive syndrome may occur as early as the fifth month or when fetal movements are first perceived, it is not usually a problem until the eighth and ninth months of pregnancy.[6 21] Finally, there may be psychological and mental factors that can influence autonomic nervous activity in the pregnant woman. As pregnancy is a joy to most women, the sense of happiness might manifest itself autonomically as increased vagal and decreased sympathetic modulation.

It has been demonstrated that higher vagal and lower sympathetic modulation can be induced by assuming the right or left lateral decubitus position in normal subjects compared with the supine position.[22] A higher venous return and less workload in the right lateral decubitus position was suggested to be responsible for this autonomic nervous system response. If the vagal enhancing and sympathetic suppressing effect of pregnancy demonstrated in the first trimester of pregnancy were caused mainly by a higher venous return as a result of increased blood volume, and less workload caused by decreased vascular resistance, the beneficial effect of the right lateral decubitus position in the first trimester should be less prominent than in non-pregnant women. Venous return has already increased and the workload of the heart has already decreased in the first trimester of pregnancy. This saturation effect may also be the reason why autonomic nervous activity in the first trimester was significantly different from that of non-pregnant controls in the supine position, but not in the right or left lateral decubitus position. The finding that the slope of the regression between $nHFP_{R/S}$ and $nHFP_S$ in the first trimester was smaller than in non-pregnant women could also be attributed to this saturation effect.

In the second trimester of pregnancy, although absolute powers of spectral heart rate variability decreased, the relative powers of spectral heart rate variability were not significantly different from that of non-pregnant controls. This could be explained by the beneficial effect of pregnancy on the autonomic nervous system in the first trimester being balanced by aortocaval compression caused by the progressively enlarging gravid uterus in the second trimester. As gestational age increases further, aortocaval compression caused by the enlarging gravid uterus further compromises venous return and cardiac output, leading to a shift in autonomic nervous activity towards an even higher sympathetic and lower vagal modulation in the third trimester of pregnancy. Similar trends in absolute powers of spectral heart rate variability were found in the study of Eneroth-Grimfors and colleagues[10]; however, normalized spectral powers and low-/high-frequency power ratios were not provided in their study.

The finding that $nHFP_{R/S}$ and $nHFP_{L/S}$ correlated negatively with $nHFP_S$ suggests that those who have higher sympathetic and lower vagal modulation in the supine position may benefit from assuming lateral decubitus positions, especially in the second and third trimesters. The relief of aortocaval compression by assuming lateral decubitus positions may be responsible for the largest slope being the regression between $nHFP_{R/S}$ or $nHFP_{L/S}$ and $nHFP_S$ in the third trimester.

In summary, we found biphasic changes in autonomic nervous activity during pregnancy. It was shifted significantly to a lower sympathetic and higher vagal activity in the first trimester of pregnancy and then to a higher sympathetic and lower vagal activity in the third trimester. The balance between the haemodynamic changes of pregnancy and aortocaval compression caused by the progressively enlarging gravid uterus may be responsible for these biphasic changes.

Acknowledgements

This work was supported by project VGHTH87-08-1 of the VGH-NTHU Joint Research Program and a research fund from Tao-Yuan General Hospital, Taiwan, Republic of China.

References

1 Elkayam U, Gleicher N. Hemodynamics and cardiac function during normal pregnancy and the puerperium. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy: Diagnosis and Management of Maternal and Fetal Disease*, 2nd Edn. New York: Alan R. Liss Inc, 1990, 5

2 Oakley CM. Cardiovascular disease in pregnancy. *Can J Cardiol* 1990; **6** (Suppl. B): 33B

3 Bryant EE, Douglas BH, Ashburn AD. Circulatory changes following prolactin administration. *Am J Obstet Gynecol* 1973; **115**: 53–7

4 Gerber JG, Payne NA, Murphy RC, Nies AS. Prostacyclin produced by the pregnant uterus in the dog may act as a circulating vasopressor substance. *J Clin Invest* 1981; **67**: 632–6

5 Metcalfe J, Ueland K. Maternal cardiovascular adjustment to pregnancy. *Prog Cardiovasc Dis* 1974; **16**: 363–74

6 Kinsella SM, Lohmann G. Supine hypotensive syndrome. *Obstet Gynecol* 1994; **3**: 774–88

7 Speranza G, Verlato G, Albiero A. Autonomic changes during pregnancy: assessment by spectral heart rate variability analysis. *J Electrocardiol* 1998; **31**: 101–9

8 Ekholm EMK, Hartiala J, Huikuri HV. Circadian rhythm of

frequency-domain measures of heart rate variability in pregnancy. *Br J Obstet Gynaecol* 1997; **104**: 825–8

9 Ekholm EMK, Erkkola RU, Piha SJ, Jalonen JO, Metsala TH, Antila K. Changes in autonomic cardiovascular control in mid-pregnancy. *Clin Physiol* 1992; **12**: 527–36

10 Eneroth-Grimfors E, Westgren M, Ericson M, Ihrman-Sandahl C, Lindblad LE. Autonomic cardiovascular control in normal and pre-eclamptic pregnancy. *Acta Obstet Gynecol Scand* 1994; **73**: 680–4

11 Ekholm EMK, Erkkola RU. Autonomic cardiovascular control in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1996; **64**. 29–36

12 Kuo C-D, Chen G-Y, Yang M-J, Tsai Y-S. The effect of position on autonomic nervous activity in late pregnancy. *Anaesthesia* 1997; **52**: 1161–5

13 Chen G-Y, Kuo C-D, Yang M-J, Lo H-M, Tsai Y-S. Comparison of supine and upright positions on the autonomic nervous activity in late pregnancy: the role of aortocaval compression. *Anaesthesia* 1999; **54**: 215–19

14 Chen G-Y, Kuo C-D, Yang M-J, Lo H-M, Tsai Y-S. The return of autonomic nervous activity after delivery: the role of aortocaval compression. *Br J Anaesth* 1999; **82**: 932–4

15 Oppenheim AV, Schafer RW. *Discrete-Time Signal Processing.* Englewood Cliffs: Prentice Hall, 1989; 581–642

16 Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981, **213**: 220–2

17 Huikuri HV, Niemela MJ, Ojala S, Rantala A, Ikaheimo MJ, Airaksinen KEJ. Circadian rhythms of frequency domain measures of heart rate variability in healthy subjects and patients with coronary artery disease: effects of arousal and upright posture. *Circulation* 1994; **90**: 121–6

18 Pomeranz B, Macaulay RJB, Caudill MA, *et al.* Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; **248**. H151–3

19 Pagani M, Lombardi F, Guzzetti S, *et al.* Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 1986; **59**. 178–93

20 Holmes F. Incidence of the supine hypotensive syndrome in late pregnancy: a clinical study in 500 subjects. *J Obstet Gynaecol Br Commonwealth* 1960; **67**: 254–8

21 Ahltorp G. On problems in the supine position in pregnant women. *Acta Obstet Gynaecol Scand* 1935–36; **15**: 295–431

22 Chen G-Y, Kuo C-D. The effect of the lateral decubitus position on vagal tone. *Anaesthesia* 1997; **52**: 653–7

British Journal of Anaesthesia **84** (3): 330–4 (2000)

Transoesophageal echocardiographic assessment of haemodynamic changes during laparoscopic herniorrhaphy in small children

S. G. Sakka[1], E. Huettemann[1]*, G. Petrat[1], A. Meier-Hellmann[1], F. Schier[2] and K. Reinhart[1]

[1]Department of Anaesthesiology and Intensive Care Medicine and [2]Department of Paediatric Surgery, Friedrich-Schiller-University of Jena, Bachstrasse 18, D-07740 Jena, Germany

**Corresponding author*

Laparoscopic techniques for surgery are gradually becoming established in paediatric surgery. Technical aspects, such as the maximum safe gas insufflation pressure, are still open to discussion. We used transoesophageal echocardiography to study the haemodynamic changes in eight small children undergoing laparoscopic herniorrhaphy, with two different levels of intra-abdominal pressure (IAP), 6 and 12 mm Hg. End-tidal carbon dioxide tension was maintained constant at 4.3–4.7 kPa. After baseline measurements, an IAP of 12 mm Hg was applied for 10 min. Next, IAP was decreased to 6 mm Hg, followed by a second period of 12 mm Hg. Haemodynamic measurements were obtained at each stage. A further measurement was obtained 10 min after abdominal deflation at the end of surgery while anaesthesia was unchanged. Cardiac index (CI) decreased significantly only after the first 12 mm Hg level of IAP. The subsequent decrease in IAP to 6 mm Hg caused return of CI to baseline levels. The second increase in IAP did not cause any reduction in CI. The initial reduction in CI, although statistically significant, did not appear to be clinically important. We conclude that an IAP of up to 12 mm Hg appeared to be safe in healthy small children undergoing laparoscopic herniorrhaphy.

Br J Anaesth 2000; **84**: 330–4

Keywords: anaesthesia, paediatric; surgery, laparoscopy; surgery, herniorrhaphy; measurement techniques, transoesophageal echocardiography; cardiovascular system, effects

Accepted for publication: October 19, 1999

Laparoscopic techniques are standard procedures in adults and are becoming established in paediatric surgery. However, several technical aspects are still open to discussion, such as the maximum gas insufflation pressure to be applied in children.[1–3] The surgeon prefers a good view and therefore higher insufflation pressures. In contrast, the anaesthetist prefers pressures as low as possible to reduce haemodynamic changes. A compromise is needed between adequate surgical conditions and haemodynamic effects.

Previous studies on the haemodynamic effects of different levels of intra-abdominal pressures (IAP), mainly in adults, are controversial, not only with respect to cardiac filling pressures but also cardiac output.[4–6] Unfortunately, variables such as positioning or volume status were either not controlled or not reported. In children, data on the haemodynamic effects of increases in IAP are limited to arterial pressure and aortic blood flow.[7–9]

Although the adverse effects of pneumoperitoneum on haemodynamics led to recommendations limiting IAP to 6 mm Hg in infants because of the risk of reopening of right–left shunts (foramen ovale) and to 12 mm Hg in older children,[10] no definitive data are available. In this study, we have investigated the effects of two different levels of IAP (6 and 12 mm Hg) on haemodynamics during laparoscopic surgery in small children.

Patients and methods

After obtaining approval from our Institutional Ethics Committee and written consent from parents, we enrolled eight small children undergoing elective laparoscopic herniorrhaphy in a prospective study. All subjects (three females, five males, aged 2–6 yr (mean 3.5 (SD 1.3) yr), weight 17 (4) kg) were ASA I. Children received tea *ad libidum* until 2 h before surgery. Oral premedication consisted of midazolam 0.5 mg kg^{-1} in 10 ml of tea. Local cutaneous anaesthesia for placement of a peripheral venous cannula was obtained with an anaesthetic dressing (EMLA, Astra Chemicals, FRG).

Anaesthesia was induced with thiopental 5 mg kg^{-1} i.v. and fentanyl 0.005 mg kg^{-1} i.v. For intubation, rocuronium 0.6 mg kg^{-1} was used. After induction of anaesthesia, a nasogastric tube was advanced to empty the stomach by suctioning and then removed. Anaesthesia was maintained

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

with 0.75 MAC of sevoflurane and 67% nitrous oxide in oxygen.[11] Neuromuscular block was monitored by transcutaneous nerve stimulation of the ulnar nerve (Stimulator NZ 252, Fisher and Paykel, New Zealand) as train-of-four (TOF). Repeated doses of rocuronium 0.1 mg kg^{-1} were given when a response to the third stimulus (75–80% neuromuscular block) was detected. During operation, all children received isotonic electrolyte solution 4 ml kg^{-1} h^{-1} in 1% glucose. Normothermia was maintained using an infusion heating system and warm touch mattress (Mallinckrodt Medical, FRG). Surgery was performed in the supine position. All children underwent mechanical ventilation using a pressure-controlled mode (AS3, Datex-Engstroem, Finland). In all patients, I:E ratio was 1:1 and end-expiratory pressure was maintained positive (PEEP) at 5 cm H_2O throughout the procedure. To avoid haemodynamic changes induced by hypercapnia, end-tidal carbon dioxide tension ($P_{E'CO_2}$) was maintained constant throughout the study at 4.3–4.7 kPa. After insufflation, ventilatory frequency was increased from 15 to 20 bpm and plateau inspiratory pressure was adjusted during the following three phases of pneumoperitoneum to maintain $P_{E'CO_2}$ constant. After deflation of the abdomen, inspiratory plateau pressure and ventilatory frequency were reduced to pre-insufflation levels.

Laparoscopic hernia repair in children has been described previously, for indirect and direct hernias.[12 13] Previously, the procedure was performed in children with 5-mm or 3-mm trocars. The technique used in our study, with 1.7-mm instruments and without trocars, is new.[13] The procedure used for laparoscopic herniorrhaphy was based on a three-puncture technique and suture of the inguinal hernia. With this technique there is virtually no surgical 'access trauma' and repair is limited to the inner inguinal ring. IAP was controlled with an electrical carbon dioxide insufflator (Electronic endosufflator No. 26430520, Storz, FRG) which allows measurement of IAP.

Haemodynamic measurements included: heart rate, systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures (measured non-invasively at the upper arm by oscillometry), $P_{E'CO_2}$ and transcutaneous peripheral oxygen saturation (S_{pO_2}). Body temperature, respiratory minute volume, airway pressures and compliance were monitored throughout (AS3, Datex-Engstroem, Finland). Because I:E ratio was 1:1, mean airway pressure (*P*mean) was calculated as: *P*mean= PEEP+inspiratory plateau pressure/2.

Transoesophageal echocardiography (TEE) was performed using a 7-mm monoplane 5-MHz paediatric probe (Hewlett Packard, USA) which was connected to a Hewlett Packard SONOS 1000. The probe was placed transorally and each time advanced into the stomach for the transgastric short axis view. All echocardiographic measurements were stored on video tape and analysed later by two independent investigators (S. G. S., E. H.). Echocardiography included a transgastric short axis view at the mid-papillary level for analysis of left ventricular end-systolic (ESD) and end-diastolic (EDD) diameters and areas (ESA, EDA), for calculation of fractional shortening (FS) and fractional area change (FAC). Cardiac output (CO) was calculated by the velocity time integral (VTI) of the pulmonary artery Doppler flow profile, its diameter (*d*) and heart rate (HR): $CO = VTI \times (d/2)^2 \times HR$. For respiratory changes in pulmonary artery flow profiles, consecutive heart beats of three respiratory cycles were analysed and averaged. Left ventricular wall thickness (WD) was determined as mean over the entire wall, and systolic wall stress (σ_{sys}) was calculated as $\sigma_{sys} = SAP \times ESD/WD$. Systemic vascular resistance (SVR) was calculated by a simplified formula according to $SVR = 80 \times MAP/CO$.

Study procedure

After induction of anaesthesia and when steady state conditions were achieved, defined as changes in MAP, heart rate, S_{pO_2}, $P_{E'CO_2}$ and expiratory anaesthesia gas concentrations of less than 10% within 10 min, the first haemodynamic measurements were obtained (baseline). Then, carbon dioxide was introduced to give an IAP of 12 mm Hg and haemodynamic measurements were repeated 10 min later (PP_1 12). The pressure was then reduced to 6 mm Hg. After a 10-min period of 6 mm Hg (PP 6), IAP was increased again to 12 mm Hg for 10 min (PP_2 12). The last haemodynamic measurement was obtained 10 min after abdominal deflation at the end of surgery while maintaining anaesthesia unchanged (control).

Data analysis

All values are expressed as mean (SD). Echocardiographic data were averaged between the two investigators. For inter-individual comparisons, left ventricular areas, systemic vascular resistance and cardiac output are expressed in relation to body surface area, calculated according to DuBois. Statistical analysis was performed using ANOVA for repeated measurements and a pairwise multiple comparison procedure (Student–Newman–Keuls method, SigmaStat). Statistical significance was considered at $P<0.05$.

Results

Results are summarized in Table 1. Significant haemodynamic changes included an increase in arterial pressure and decreases in heart rate and CI during the first increase in IAP to 12 mm Hg compared with baseline. After decreasing IAP to 6 mm Hg, CI returned to baseline levels. The second increase in IAP to 12 mm Hg did not cause any reduction in CI. Global left ventricular systolic function, as expressed by fractional shortening, was significantly lower at both 12 mm Hg levels, whereas values at 6 mm Hg were not significantly different from baseline or control. However, fractional area change did not change significantly under the various conditions.

Table 1 Haemodynamic and respiratory changes (mean (SD)). PP$_1$ 12=First IAP level of 12 mm Hg, PP 6=IAP of 6 mm Hg, PP$_2$ 12=second IAP level of 12 mm Hg. SAP=Systolic arterial pressure, DAP=diastolic arterial pressure, MAP=mean arterial pressure, HR=heart rate, ESAI=end-systolic area index, EDAI=end-diastolic area index, σ_{sys}=left ventricular systolic wall stress, CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance index, FS=fractional shortening, FAC=fractional area change, *P*mean=mean airway pressure, MV=respiratory minute volume, $P\text{E}'_{CO_2}$= end-tidal carbon dioxide tension, *C*=airway compliance. Significant difference ($P<0.05$) compared with *baseline; †PP$_1$ 12, ‡PP 6; §PP$_2$ 12

	Baseline	PP$_1$ 12	PP 6	PP$_2$ 12	Control
SAP (mm Hg)	92 (10)	108 (17)*	100 (15)*†	105 (16)*	93 (12)†‡§
DAP (mm Hg)	53 (7)	65 (13)*	59 (9)	62 (10)*	54 (6)†§
MAP (mm Hg)	68 (7)	80 (13)*	73 (10)†	77 (12)*	69 (8)†§
HR (beat min^{-1})	112 (11)	104 (11)*	106 (7)*	108 (10)	104 (11)*
ESAI (cm^2 m^{-2})	5.4 (1.3)	6.7 (1.4)*	6.0 (1.2)	6.4 (0.9)*	5.1 (1.4)†§
EDAI (cm^2 m^{-2})	9.4 (1.5)	11.2 (2.0)*	10.6 (1.6)	11.1 (1.7)	9.6 (2.0)†
σ_{sys} (mm Hg)	299 (58)	426 (69)*	360 (57)*†	407 (76)*‡	301 (70)†‡§
CI (litre min^{-1} m^{-2})	4.6 (0.6)	4.0 (0.4)*	4.6 (0.7)†	4.4 (0.8)	4.7 (0.6)†
SVI (ml m^{-2})	41 (7)	39 (5)	43 (6)†	41 (8)	45 (8)*†§
SVRI (dyn s cm^{-5} m^{-2})	1227 (317)	1617 (392)*	1313 (336)†	1461 (470)*†‡	1209 (279)†§
FS (%)	31.0 (6.0)	26.5 (5.4)*	28.4 (4.3)*	27.4 (5.9)*	31.4 (5.2)†‡§
FAC (%)	43.3 (8.5)	39.8 (11.7)	43.4 (6.2)	42.0 (8.6)	46.8 (8.2)
*P*mean (cm H$_2$O)	13.0 (0.6)	15.7 (1.4)*	14.0 (0.8)†	15.8 (1.4)*‡	13.4 (0.8)†§
MV (litre min^{-1})	3.2 (0.7)	3.7 (0.8)*	3.7 (0.6)*	3.9 (0.5)*	3.3 (0.4)†‡§
$P\text{E}'_{CO_2}$ (kPa)	4.4 (0.1)	4.4 (0.1)	4.4 (0.1)	4.4 (0.1)	4.3 (0.1)
C (ml cm H$_2$O^{-1})	19 (3)	12 (3)*	15 (3)*	12 (3)*	19 (2)

Discussion

We found a decrease in CI of approximately 13% at an IAP of 12 mm Hg in healthy children undergoing laparoscopic herniorrhaphy. Reduction of IAP to 6 mm Hg was associated with return of CI to baseline levels which may indicate that an IAP of 6 mm Hg does not cause haemodynamic effects in otherwise healthy children. Left ventricular systolic function was diminished at an IAP level of 12 mm Hg, as indicated by a significant decrease in fractional shortening and a tendency to a reduction in fractional area change. Similar to changes in CI, after decreasing IAP to 6 mm Hg, fractional shortening values returned to baseline.

Recommendations for a maximum IAP during laparoscopic surgery are limited to adults. According to the current literature, a level of 14 mm Hg or higher in adults is considered to have an important effect on global haemodynamics[5] and should be avoided. In that study,[5] all patients were in a 10° head-up position, and CI decreased by approximately 18% from before abdominal insufflation to 5 min of pneumoperitoneum. Interestingly, CI recovered to pre-insufflation values after 15 and 30 min of pneumoperitoneum.[5] In pigs, CI was preserved during ventilation with a PEEP of 5 cm H$_2$O but significantly decreased when an IAP of 15 mm Hg was added.[14]

In piglets with a body weight of 4–6 kg,[15] the haemodynamic effects of a capnoperitoneum were studied with an IAP of 15 mm Hg before and after 1 h of insufflation. In one group of animals, when arterial carbon dioxide tension was allowed to increase (up to 6.4 kPa), CI increased, probably from hypercapnia.[16] In a second group, arterial carbon dioxide tension was maintained constant by hyperventilation and CI remained unchanged, supporting the hypothesis that an IAP of 15 mm Hg does not impair haemodynamics in children.

In contrast, in a clinical study in which $P\text{E}'_{CO_2}$ was kept constant, cardiac output, as measured by aortic flow from transoesophageal echo-Doppler, decreased by approximately 30% during an IAP of 10 mm Hg in 12 infants and small children (6–30 months).[9] Haemodynamic measurements were performed before, after 5 min of insufflation and 5 min after deflation. A limitation of this study might be that measurement in the abdominal aorta overestimates the decrease in cardiac output because the increase in IAP causes redistribution of blood flow from the lower to the upper extremities. Nevertheless, as the patients studied by Gueugniaud and colleagues[9] were younger, their data may indicate a higher susceptibility of infants to preload changes.

We carefully maintained $P\text{E}'_{CO_2}$ constant by increasing the inspiratory airway pressure during pneumoperitoneum, as in other studies.[5 9 17] As mean airway pressure was increased on average by 3 cm H$_2$O, the increase in intrathoracic pressure could have influenced cardiac loading conditions[18] and thus cardiac output. The increase in left ventricular afterload (i.e. MAP) during pneumoperitoneum in our study was associated with an increase in left ventricular areas, which could indicate adaptive mechanisms and does not support impairment in left ventricular filling from increased intrathoracic pressure. In our study, we relied on measurement of end-tidal carbon dioxide tension for two reasons: first, to avoid placing an arterial cannula which is an invasive procedure, and second, at least in adults during pneumoperitoneum,[19–21] changes in $P\text{E}'_{CO_2}$ parallel changes in arterial carbon dioxide tension over a wide range of values.

For comparison of the echocardiographic changes during pneumoperitoneum, we referred to adequately designed studies that excluded the well known side effects of hypercapnia on cardiac function.[16] In healthy adults,[17] echocardiography revealed that left ventricular systolic function was preserved during capnoperitoneum with an IAP of 15 mm Hg. However, end-systolic and end-diastolic areas increased non-significantly after 5 min of carbon dioxide insufflation, while systemic arterial pressure increased significantly. Left ventricular end-systolic wall stress and left ventricular ejection fraction were slightly increased. In contrast, Dorsay, Greene and Baysinger[22] found a decrease in left ventricular end-diastolic volume during an IAP of 15 mm Hg, which further decreased during reverse Trendelenburg positioning. CI and left ventricular ejection fraction first remained preserved, but decreased during tilting. Unfortunately, only long axis views were obtained which may lead to incorrect results from changes in position of the heart during pneumoperitoneum. Myre and colleagues[23] studied adults undergoing laparoscopic cholecystectomy using an IAP of 15 mm Hg. In their results, arterial pressure increased significantly while CI remained unchanged. However, analysis of left ventricular long-axis views yielded no significant changes in left ventricular end-diastolic areas.

In our study, we used pulmonary artery Doppler flow for calculation of cardiac output. The accuracy of this approach has been investigated extensively in clinical studies. In a validation study, Savino and colleagues[24] found excellent agreement between pulmonary artery Doppler flow-derived cardiac output and the current standard (i.e. the pulmonary artery thermodilution technique). Furthermore, Vanzetto and colleagues[25] compared pulmonary artery Doppler flow-derived cardiac output values with those obtained from aortic or mitral valve Doppler flow in 100 consecutive patients and reported good agreement (r=0.96). In a study on the haemodynamic effects of halothane and isoflurane, Murray, Forbes and Mahoney[26] used this technique for measurement of cardiac output in neonates and infants.

In our subjects, all supine, we found a decrease in CI only for the first 12 mm Hg period of IAP, and this was not seen during a second increase in IAP to 12 mm Hg. Furthermore, stroke volume index was not different between baseline and the first 12 mm Hg period of IAP. Accordingly, the reduction in CI was related more to the reduction in heart rate, which is a known cardiovascular response to cross clamping of the abdominal aorta and the acute increase in left ventricular afterload.[27]

In all children, we applied PEEP 5 cm H_2O which may not be common clinical practice. However, we wished to prevent alveolar collapse from increased IAP as has been suggested by Pighin and colleagues[28] who stressed that functional residual capacity is less in small children and hypoxaemia may develop faster. Another reason to apply PEEP during pneumoperitoneum is to reduce the risk of an air embolism.[29] In adults, a PEEP of even 10 cm H_2O does not decrease cardiac output.[30] Our study design failed to provide any information on adaptive mechanisms. Therefore, future studies should investigate the effects of pneumoperitoneum over time in small children.

In summary, we found that an IAP of 6 mm Hg appeared to be safe in children to avoid haemodynamic alterations while still allowing operating conditions that were judged satisfactory by our surgeons. As a reduction in CI of 13% does not present a substantial risk to a healthy child, an IAP of 12 mm Hg could be used. Perhaps in children with cardiocirculatory difficulty, an IAP of 6 mm Hg, at least initially, should be preferred. In those children, transoesophageal echocardiography, which allows rapid cardiac assessment during surgery, may assist intraoperative monitoring.

References

1 Manner T, Aantaa R, Alanen M. Lung compliance during laparoscopic surgery in paediatric patients. *Paediatr Anaesth* 1998; **8**: 25–9

2 Hasegawa T, Miki Y, Yoshiaka Y, Mizutani S, Sasaki T, Sumimura J. Laparoscopic diagnosis of blunt abdominal trauma in children. *Paediatr Surg Int* 1997; **12**: 132–6

3 Rubin SZ, Davis GM, Sehgal Y, Kaminski MJ. Does laparoscopy adversely affect gas exchange and pulmonary mechanics in the newborn? An experimental study. *J Laparoendosc Surg* 1996, **6** (Suppl. 1): S69–73

4 Kelman GR, Swapp GH, Smith I, Benzie RJ, Gordon NLM. Cardiac output and arterial blood-gas tension during laparoscopy *Br J Anaesth* 1972; **44**: 1155–62

5 Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Hemodynamic changes during laparoscopic cholecystectomy *Anesth Analg* 1993; **76**: 1067–71

6 Feig BW, Berger DH, Dougherty TB, *et al.* Pharmacologic intervention can reestablish baseline hemodynamic parameters during laparoscopy. *Surgery* 1994; **116**: 733–41

7 Sfez M, Guérard A, Desruelle P. Cardiorespiratory changes during laparoscopic fundoplication in children. *Paediatr Anaesth* 1995; **5**. 89–95

8 Hsing C-H, Hseu S-S, Tsai C-C, Chen T-W, Wei C-F, Lee T-Y. The physiological effect of CO_2 pneumoperitoneum in paediatric laparoscopy. *Acta Anaesthesiol Sin* 1995; **33**: 1–6

9 Gueugniaud P-Y, Abisseror M, Moussa M, Foussat C, Petit P, Dodat H. The hemodynamic effects of pneumoperitoneum during laparoscopic surgery in healthy infants· assessment by continuous esophageal aortic blood flow echo-Doppler *Anesth Analg* 1998; **86**: 290–3

10 Rubin SZ, Davis MG. Pneumoperitoneum in the pediatric age. In: Rosenthal RJ, Friedman RL, Phillips EH, eds. *The Pathophysiology of Pneumoperitoneum*. Berlin: Springer-Verlag, 1998; 159–67

11 Sarner JB, Levine M, Davis PJ, Lerman J, Cook DR, Motoyama EK. Clinical characteristics of sevoflurane in children A comparison with halothane. *Anesthesiology* 1995; **82**: 38–46

12 Montupet P, Esposito C, Roblot-Maigret B, Desruelle P. Laparoscopic repair of direct inguinal hernia in childhood. *Pediatr Endosurg Innov Techniques* 1998; **2**: 69–72

13 Schier F. Laparoscopic herniorrhaphy in girls. *J Pediatr Surg* 1998; **33**: 1495–7

14 Moffa SM, Quinn JV, Slotman GJ Hemodynamic effects of carbon dioxide pneumoperitoneum during mechanical ventilation and positive end-expiratory pressure. *J Trauma* 1993; **35**: 613–17

15 Graham AJ, Jirsch DW, Barrington KJ, Hayashi AH. Effects of intraabdominal CO_2 insufflation in the piglet. *J Pediatr Surg* 1994; **29**: 1276–80

16 Rasmussen JP, Dauchot PJ, DePalma RG, *et al.* Cardiac function and hypercarbia. *Arch Surg* 1978; **113**: 1196–200

17 Cunningham AJ, Turner J, Rosenbaum S, Rafferty T. Transoesophageal echocardiographic assessment of haemodynamic function during laparoscopic cholecystectomy. *Br J Anaesth* 1993; **70**: 621–5

18 Dhainaut J, Devaux JY, Monsallier JF, Bruner F, Villemant D, Huyghebaert MF. Mechanics of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. *Chest* 1986; **90**: 74–80

19 Fujii Y, Tanaka H, Tsurukoa S, Toyooka H, Amaha K. Middle cerebral arterial blood flow velocity increases during laparoscopic cholecystectomy. *Anesth Analg* 1994, **78**: 80–3

20 Nyarwaya JB, Mazoit JX, Samii K. Are pulse oximetry and end-tidal carbon dioxide tension monitoring reliable during laparoscopic surgery? *Anesthesia* 1994; **49**: 775–8

21 Kazama T, Ikeda K, Kato T, Kikura M. Carbon dioxide output in laparoscopic cholecystectomy. *Br J Anaesth* 1996; **76**: 530–5

22 Dorsay DA, Greene FL, Baysinger CL. Hemodynamic changes during laparoscopic cholecystectomy monitored with transesophageal echocardiography. *Surg Endosc* 1995; **9**: 128–34

23 Myre K, Buanes T, Smith G, Stokland O. Simultaneous hemodynamic and echocardiographic changes during abdominal gas inflation. *Surg Laparosc Endosc* 1997; **7**: 415–19

24 Savino JS, Troianos CA, Aukburg S, Weiss R, Reichek N. Measurement of pulmonary blood flow with transesophageal two-dimensional and Doppler echocardiography. *Anesthesiology* 1991; **75**: 445–51

25 Vanzetto G, Denis B, Mann H, *et al.* Feasibility and accuracy of pulmonary blood flow measurement by Doppler echocardiography. Apropos of 100 consecutive cases. *Arch Mal Coeur Vaiss* 1994; **87**: 499–506

26 Murray DJ, Forbes RB, Mahoney LT. Comparative hemodynamic depression of halothane versus isoflurane in neonates and infants: an echocardiographic study. *Anesth Analg* 1992: **74**: 329–37

27 Gooding JM, Archie JP Jr, McDowell H. Hemodynamic response to infrarenal aortic cross-clamping in patients with and without coronary artery disease. *Crit Care Med* 1980; **8**: 382–5

28 Pighin G, Crozier TA, Weyland W, Ludtke FE, Kettler D. Specifics in anesthesiology in laparoscopic surgery in infancy. *Zentralbl Chir* 1993; **118**: 628–30

29 Fahy BG, Hasnain JU, Flowers JL, Plotkin JS, Odonkor P, Ferguson MK. Transesophageal echocardiographic detection of gas embolism and valvular dysfunction during laparoscopic nephrectomy. *Anesth Analg* 1999; **88**: 500–4

30 Kraut EJ, Anderson JT, Safwat A, Barbosa R, Wolfe BM. Impairment of cardiac performance by laparoscopy in patients receiving positive end-expiratory pressure. *Arch Surg* 1999; **134**: 76–80

British Journal of Anaesthesia **84** (3). 335–40 (2000)

Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine *vs* midazolam or ketamine alone†

W. Funk*, W. Jakob, T. Riedl and K. Taeger

Department of Anaesthesiology, University of Regensburg, 93042 Regensburg, Germany
**Corresponding author*

Anxiolysis and sedation with oral midazolam are common practice in paediatric anaesthesia. However, good or excellent results are seen in only 50–80% of cases. For this reason, we investigated if addition of a low dose of oral ketamine (MIKE: ketamine 3 mg kg^{-1}, midazolam 0.5 mg kg^{-1}) resulted in better premedication compared with oral midazolam 0.5 mg kg^{-1} or ketamine 6 mg kg^{-1} alone, in a prospective, randomized, double-blind study. We studied 120 children (mean age 5.7 (range 2–10) yr) undergoing surgery of more than 30 min duration. After oral premedication in the ward and transfer, the child's condition in the induction room was evaluated by assigning 1–4 points to the quality of anxiolysis, sedation, behaviour at separation from parent and during venepuncture (transfer score). On days 1 and 7 after operation, parents were interviewed for changes in behaviour (eating, sleep, dreams, toilet training), recollection and satisfaction, using a standardized questionnaire. The groups were similar in age, sex, weight, intervention and duration of anaesthesia. The transfer score was significantly better in the MIKE group (12.5 (95% confidence interval (CI) 11.9–13.1)) than in the ketamine or midazolam groups (10.6 (9.8–11.4) and 11.5 (10.7–12.3), respectively). Success rates for anxiolysis and behaviour at separation were greater than 90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone. The incidence of salivation, excitation and psychotic symptoms was low in all groups. Vertigo and emesis before induction were significantly more frequent after ketamine premedication. During recovery, there were no differences in sedation or time of possible discharge. After 1 week, parents reported nightmares (ketamine five, midazolam three, MIKE one), restless sleep (five/four/four) or negative memories (three/four/one). There were no major or continuing disturbances in behaviour or development. In summary, significantly better anxiolysis and separation were observed with a combination of ketamine and midazolam, even in awake children (sedation was not successful according to the preset criteria), than with midazolam or ketamine alone. Duration of action and side effects of the combination were similar to those of midazolam. The combination of both drugs in strawberry flavoured glucose syrup (pH 4.5 approximately) is chemically stable for 8 weeks.

Br J Anaesth 2000; **84**: 335–40

Keywords: premedication, midazolam; premedication, ketamine; sedation; children

Accepted for publication: October 4, 1999

Anxiolysis and sedation using preoperative medication is still common practice in paediatric anaesthesia.[1] Key features of good premedication are easy application, rapid onset, short duration of action and lack of significant side effects. Midazolam meets these criteria with its multiple routes of administration (oral, rectal, nasal), an onset time of 10–20 min, duration of action of approximately 30 min[2] and no interference with vital signs in doses less than 0.5 mg kg^{-1}.[3] Therefore, it has become the most widely used paediatric premedication in Europe and the USA.[4 5] However, good or excellent results are seen in only 60–80% of cases.[3 6 7] In our own young patients presenting for dental repair, the success rate was even lower (50%).

Ketamine has similar pharmacodynamics[8] after oral administration and has been investigated as an alternative premedication.[9–11] In these studies, doses of 3–6 mg kg^{-1} were used. The authors reported a high overall success rate without significant side effects. However, it is widely acknowledged that ketamine i.v. or i.m. causes hallucina-

---

†Part of this work originates from the dissertation of T Riedl (unpublished).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

tions in many patients. Even subanaesthetic concentrations of ketamine produce psychedelic effects when given i.v.[12] There are no such data in paediatric patients for oral administration, following which there is a high first pass metabolism.[8] The metabolite norketamine causes sedation and analgesia also, but little is known of its side effects. A comparative study of oral ketamine or midazolam in children was aborted after undesirable side effects from ketamine 6 mg kg^{-1}, including increased secretions, hallucinations and dysphoria.[13] Beebe and colleagues[14] were the first to compare a combination of rectal midazolam 0.5 mg kg^{-1} and rectal ketamine 3 mg kg^{-1} with both drugs given alone. They found that both midazolam alone and the combination were equally useful techniques when i.v. induction of anaesthesia was desired. Psychotomimetic side effects were not addressed. Another study by Warner, Cabaret and Velling[6] compared midazolam 0.5 mg kg^{-1} orally with either ketamine 6 mg kg^{-1} orally or a combination (0.4 and 4 mg kg^{-1}), and found the mixture to be the most effective premedicant as judged by ease of separation and mask acceptance. They stated that 'no psychological disturbances were noted in the immediate postoperative period', but gave no details on the method of assessment.

Considering the small data base and lack of studies on possible psychotomimetic side effects, we have investigated if the combination of a low dose of oral ketamine with midazolam provides better premedication than either oral midazolam or ketamine alone, in a prospective, randomized, double-blind study. With the intention of maintaining the anxiolysis provided by midazolam and adding the sedative and analgesic qualities of ketamine without psychedelic side effects, we chose to combine midazolam 0.5 mg kg^{-1} with ketamine 3 mg kg^{-1}.

Patients and methods

After obtaining approval from the Ethics Committee of the Medical Faculty, we studied 120 healthy children (ASA I/II), aged 2–10 yr, undergoing surgery of more than 30 min expected duration. Exclusion criteria were ASA III or higher, severe dysfunction of the CNS or increased intracranial pressure, malformations of the cardiovascular system, hypertonus, hyperthyroidism and long-term therapy with theophylline or hepatic enzyme-inducing drugs. Informed parental consent was obtained at least 24 h before the start of operation. Children were allocated to one of three study groups using computer-generated random numbers (MS-EXCEL): group 1 received midazolam 0.5 ml kg^{-1}, group 2 was given ketamine 6 mg kg^{-1} and group 3 received midazolam 0.5 mg kg^{-1} with ketamine 3 mg kg^{-1} (MIKE). Medications were prepared by the pharmacist according to the randomized sequence using strawberry flavoured glucose syrup as a carrier and filled into bottles containing 12.5 ml (maximum dose) tagged with the study number only. The combination of both drugs in glucose syrup (pH 4.5 approximately) is chemically stable for 8 weeks (own data, remaining activity >90% for both, HPLC). Concentrations of midazolam and ketamine were chosen to result in doses of 0.5 ml kg^{-1} body weight.

Table 1 Scoring of sedation and emotional status in the ward

Score	Sedation	Emotional status
1	Alert	Combative
2	Awake	Tearful
3	Drowsy	Calm
4	Asleep	Amiable

One to two hours before surgery, a mixture of local anaesthetics (EMLA, Astra Chemicals, Germany) was applied to possible sites of venepuncture. Thirty minutes before induction, premedication was given in the presence of one of the investigators (T. R.). Patients who refused to take the whole dose were excluded from further analysis. Before medication and every 5 min thereafter, sedation and emotional status were assessed using the descriptions given in Table 1.

Twenty minutes after oral premedication in the ward, children were transferred with a parent to the operating room entrance. The child's condition was evaluated after 30 min by the anaesthetist on duty with a scale assigning 1–4 points to the quality of sedation and anxiolysis, behaviour at separation from parent and during venepuncture using the terms given in Table 2. Scoring of sedation, anxiolysis and behaviour was performed immediately after the parents were out of sight, with no further transfer. Venepuncture was done approximately 5 min later in the induction room.

The scores were adopted from published studies investigating paediatric premedication.[9 14–17] Similar scores are used commonly to reduce subjectivity but are not validated in a strict sense for this or any other paediatric age group. For statistical evaluation, the scores were condensed to a dichotomous variable consisting of success (scores 3 and 4) or no success (scores 1 and 2). Furthermore, the items of the evaluation at entrance to the operating room were combined by simple addition to a single variable called transfer score (4–16 points).

In 111 children, anaesthesia was induced with propofol 2–3 mg kg^{-1} i.v.; two patients had inhalation induction with sevoflurane. Anaesthesia was maintained according to the anaesthetist's usual practice with propofol or sevoflurane, mivacurium and alfentanil, as needed. Postanaesthetic recovery was evaluated using a modified Aldrete score[18] every 10 min. A score of 9 points was considered sufficient for discharge to the ward. On days 1 and 7 after operation, parents were interviewed either in person (day 1) or by telephone (day 7) for changes in behaviour (eating, sleep, dreams, toilet training), quality of recollection and satisfaction using the questionnaire shown in Table 3. The content of recollections was assessed by age-appropriate questions about puncture, induction or surroundings. Parents were

Table 2 Scoring of sedation, emotional status and behaviour during separation from parent and on venepuncture. Patients with a score of 1 and 2 were combined for evaluation as 'no success', and those with scores of 3 and 4 as 'success'

Score	Sedation	Anxiolysis	Separation	Puncture
1	Alert	Panicky	Combative, clinging	Fight w/o success
2	Awake	Moaning	Anxious, consolable	Fight with success
3	Drowsy	Composed	Calm	Minor resistance
4	Asleep	Friendly	Sleeping	No reaction

Table 3 Assessment of postanaesthetic course on days 1 and 7 after operation

Sleep	Wakes up often	Restless	Like before	Better
Dreams	Nightmares	Negative	None	Positive
Continence	New encopresis	New enuresis	No change	Better
Eating	Refusal	New habits	No change	Better
Recollection	Negative	Indifferent	None	Positive
Development	Regression		No change	New achievements
Same procedure if needed?	Never again	Other	Indifferent	Yes

Table 4 Patient characteristics (mean (SD or range) or number)

	Age (yr)	Weight (kg)	Sex (M/F)	OR time (min)
Ketamine (n=36)	5.8 (2.2–9.8)	20.8 (4.8)	14/22	93 (39)
Midazolam (n=38)	5.7 (2.5–10.1)	19.6 (4.7)	19/19	88 (48)
MIKE (n=39)	5.7 (2.0–9.3)	19.6 (4.6)	17/22	93 (61)

informed about the date of the interviews, but not about the questions to be asked.

Sample size determination and statistical analysis

The study was designed to detect an increase in success rate from 65% to 90% with a power of 80% and an alpha error of less than 5%. Success was defined as a score of 3 or 4 for the items 'sedation', 'anxiolysis' and 'separation'. The 65% success rate was taken from a pilot study using our routine premedication with midazolam 0.5 mg kg^{-1} (n= 20). A success rate of 90% was seen as a clinically meaningful improvement justifying addition of ketamine. Using an empirical calculation given by Lerman,[19 20] sample size was estimated as 40 patients in each group for comparison of midazolam and the combination. Another 40 patients were included as a control group receiving ketamine only. For evaluation of the proportion of successful premedications, non-parametric one-way analysis of variance (Kruskal–Wallis) was used followed by chi-square tests for 'success', side effects, sex and operative procedure. To identify differences in age, weight and transfer score, Wilcoxon's rank sum test was applied. The time course of sedation in the ward was analysed using Duncan's multiple range test.[21]

Results

Groups were comparable in age, sex, weight, intervention and duration of anaesthesia (Table 4). Age variance was the same in all three groups. Operative procedures were evenly distributed and included strabismus correction (56%), dental repair (17%), tonsillectomy (17%) and laser coagulation of port wine stains (10%). Seven patients were excluded: six children did not drink the total volume and one child did not have surgery on the same day.

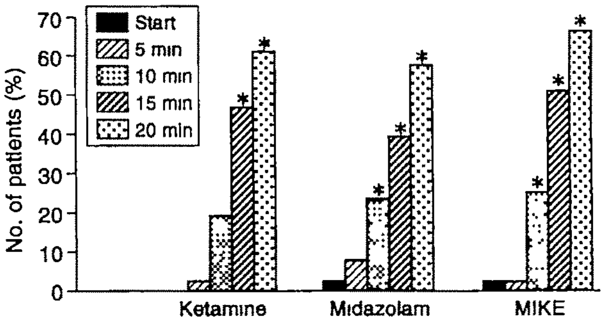


Fig 1 Proportion of children in the ketamine, midazolam and MIKE groups successfully sedated depicted over time. *Significant differences (P<0.05) compared with the initial state. At 20 min, transfer to the operating room was started.

Time course of effects

After just 10 min, an increase in the proportion of successfully premedicated children was observed. After 20 min, transfer was initiated. At this time, approximately 60% of children were sedated successfully (Fig. 1). Success was independent of the substance used. Based on our method of judgement, the time course of the effects was similar in the three groups. No differences were found in emotional status. Most children were calm or even amiable before ingestion of the syrup.

Transfer score and success of premedication

On transfer, patients were scored by the anaesthetist on duty who was unaware of the substances used and time of

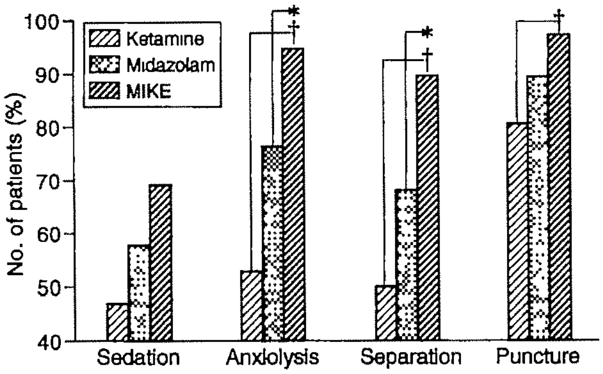


Fig 2 Success rates for sedation, anxiolysis, separation and venepuncture before induction of anaesthesia in the ketamine, midazolam and MIKE groups (success=score of 3 or 4, see text) *†Significant differences ($P<0.05$) between groups.

application. The transfer score at this time was significantly better in the MIKE group (median 13 (range 4–16)) than in the ketamine or midazolam groups (11 (4–15) and 12 (4–15)). Success rates for anxiolysis and behaviour at separation were greater than 90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone (ns) (Fig. 2). The success rate of sedation was low in all groups. However, the sedation score used in this study classifies an awake state as no success. Venepuncture was painless for most patients probably because of the use of EMLA cream, with no difference between midazolam and the combination.

Side effects

Clinically significant side effects were observed only with ketamine (Table 5). One child vomited during induction but had an uneventful recovery. The increased incidence of emesis and vertigo ($P<0.05$ *vs* midazolam and MIKE) caused severe discomfort and was probably responsible for the low success rate in the ketamine group. Psychedelic symptoms ('high')[12] such as visual or auditory hallucinations, altered sensations of self or surrounding during recovery, or parent reports of unusual behaviour (anxiety, happiness) were assessed as free observations by a single investigator (T. R.). No differences were found between groups. Salivation was similar with all premedicants and was not of concern during induction of anaesthesia. Oxygen saturation before induction was ⩾97% in all children. Excessive sedation did not occur.

Postanaesthetic recovery

During recovery from anaesthesia, no differences were observed in times to extubation and possible discharge, as assessed by an Aldrete score of 9 or 10 points[18] (Table 6). More children vomited during early recovery with ketamine. Statistical evaluation of the incidence of PONV during the first 24 h revealed no difference.

One day after anaesthesia, some children had restless sleep, nocturia or bad dreams, but there were no significant differences between the three groups. Almost 50% of patients had complete amnesia for the time between leaving the ward and reunion with the parent in the recovery room (Table 7). To investigate the quality of recollections, children were asked for specific features of rooms, wall paints, colour of blankets and clothes, anaesthesia machines, specific sounds, circumstances of venepuncture and induction, pain and anxiety. Only very few children remembered pain or other negative feelings, and there was no difference between groups. One week later, most children had resumed their previous routines. There were no signs of regression, despite two instances of new, transient nocturia. Parents reported restless sleep but no bad dreams in approximately 10% of patients. Nine children had one or more episodes of nightmares during the first week. Differences in the incidence of this event between groups were not statistically significant. Only two children had nightmares for more than 4 days (one after midazolam, one after MIKE) which both continued for 2 weeks. Thereafter, sleep returned to normal. After 1 week, only eight of 113 children had a negative recollection of the anaesthetic procedure.

Discussion

Our study provides evidence that a combination of midazolam and ketamine results in better premedication than the individual drugs given alone. The study was performed at a large university hospital treating predominantly adult patients. Our facility does not include specifically equipped child care areas. Only a few members of the anaesthesia team have long-term experience in paediatric anaesthesia. For these reasons, and in accordance with the ethics committee, we decided not to include a placebo control. The majority of specialized hospitals in Germany (>95%) use midazolam as premedication.[4] Most parents expect premedication for their children because of previous experience or information available to the public. In contrast, a 1990 review of placebo-controlled studies on pre-induction behaviour in children[22] reported satisfactory behaviour of 52–92% (median 71%) of patients allocated randomly to oral placebo premedication. There was no proof for the superiority of midazolam over placebo. Since 1990, several studies have been published demonstrating a slight advantage of midazolam over placebo.[3 15 23] Others found no difference.[16] A smooth transition from parental care to nurse and physician care and back is dependent on individual institution and patient factors, rendering comparison of different studies difficult. In addition, differences in the scores used impede direct comparison. With midazolam 0.5 mg kg^{-1}, investigators from the Hospital for Sick Children in Toronto[3] found a comparably low success rate for sedation using the same score. However, anxiolysis (score comparable with our 'separation') in their study was very successful. In our environment, separations after midazolam premedication were unsatisfactory and prompted us to investigate another regimen.

Table 5 Side effects of oral premedication before induction of anaesthesia (number of patients). 'High' indicates any type of psychedelic symptoms,[12] such as visual or auditory hallucinations, altered sensations of self or surrounding, or parent reports of unusual behaviour *Significant difference from the two other groups

	n	Nausea	Emesis	Vertigo	'High'	Excitation	Salivation
Ketamine	36	2	4*	7*	5	1	7
Midazolam	38	0	0	1	3	1	6
MIKE	39	0	0	2	3	0	7

Table 6 Recovery. Times from end of operation to extubation and discharge (mean (SD)) Postoperative nausea and vomiting in the postanaesthesia care unit and during the first day (PONV 24 h, includes PACU) *Significant difference from the two other groups

	Extubation (min)	Discharge (min)	Nausea (*n*)	Vomiting (*n*)	PONV 24 h (*n* (%))
Ketamine	18 (14)	70 (30)	2	5*	9 (25)
Midazolam	16 (11)	71 (28)	1	1	6 (16)
MIKE	16 (11)	72 (33)	1	0	4 (10)

Table 7 Summary of the interviews performed on days 1 and 7 after anaesthesia (number of children in each group)

	Ketamine (*n* = 36)	Midazolam (*n* = 38)	MIKE (*n* = 39)
Day 1			
Restless sleep	7	6	9
Nightmares	4	2	2
Nocturia	1	1	0
Parental discontent	2	1	3
Complete amnesia	14	21	19
Recollections	21	17	19
OR surroundings	6	9	15
Puncture/induction	13	7	5
Pain	1	1	0
Negative memories	5	2	2
Day 7			
Restless sleep	5	4	4
Nightmares	5	3	1
New nocturia	1	0	1
Regression	0	0	0
Negative memories	3	4	1

Oral ketamine was used in the 1970s by dentists to facilitate the treatment of mentally handicapped children. In 1982, Cetina[24] found that rectal or oral preanaesthetic medication with ketamine 15 mg kg^{-1} combined with droperidol was superior to i.m. or i.v. premedication. At first glance, 15 mg kg^{-1} seems to be a very high dose, but only 16% of oral ketamine is bioavailable because of high hepatic first pass metabolism.[8] Part of the clinical effects of oral ketamine are attributed to its metabolite norketamine which has approximately one-third the potency, but reaches higher blood concentrations. An early controlled and blinded study was published by Steward and colleagues[25] in 1990. They found that a combination of ketamine 10 mg kg^{-1} and trimeprazine was superior to morphine and trimeprazine in paediatric cardiac surgery. Gutstein and colleagues[9] compared oral premedication with ketamine 3 or 6 mg kg^{-1}, in a blinded, randomized, placebo-controlled study. With 3 mg kg^{-1}, 73% of their children were sleepy or asleep after 30 min (100% with 6 mg kg^{-1}). Significant side effects were not observed. Sekerci and colleagues[11] presented a similar study in 1996. They observed 80% successful separations with ketamine 3 mg kg^{-1}. Ketamine 6 mg kg^{-1} did not improve success but increased side effects such as nystagmus and vomiting. We were unable to reproduce the success of these studies in our ketamine group (6 mg kg^{-1}) and have no obvious explanation. Alderson and Lerman[17] compared ketamine 5 mg kg^{-1} with midazolam 0.5 mg kg^{-1} and reported similar clinical characteristics. However, as in our study, more children were tearful at separation and induction in the ketamine group No significant side effects were observed.

Not many clinicians have tried ketamine as a single drug because of the well known side effects of i.v. administration. Similar side effects have been published for oral administration.[13 26] Even subanaesthetic plasma concentrations produced psychedelic effects in volunteers.[12] A combination with a minor tranquillizer seems to be a logical answer to this problem and could at the same time broaden the pharmacodynamic profile.

The combination of ketamine and midazolam was described initially in 1992 by Beebe and co-workers[14] for rectal, and in 1993 by Lin, Moynihan and Hackel[27] for oral administration. Both groups used a combination of midazolam 0.5 mg kg^{-1} with ketamine 3 mg kg^{-1}. In Beebe's study,[14] separation was satisfactory with midazolam in 92% of cases and in 100% with the combination (ns), but in only 60% with ketamine alone. Complications were low and similar between groups. Psychedelic side effects were not addressed by the investigators. Lin, Moynihan and Hackel[27] reported no difference in behaviour at separation or induction after administration of midazolam 0.75 mg kg^{-1}, ketamine 6 mg kg^{-1} or the same combination, as in our study. Their success rate using the combination was about 80% at separation and 70% at induction. However, they found a faster onset time (*vs* both other groups), less oral secretions and nystagmus (*vs* ketamine) and faster recovery (*vs* midazolam). No postoperative complications, such as dreaming or nightmares, were observed. Warner, Cabaret and Velling[6] found that a mixture of midazolam 0.4 mg kg^{-1} and ketamine 4 mg kg^{-1} was significantly more effective than midazolam 0.5 mg kg^{-1} or ketamine 6 mg kg^{-1} alone in their partially blinded study. They noted no psychological disturbances in the immediate postoperative period but gave no details about the evaluation of this crucial issue.

It has been suggested that oral rather than i.m. ketamine should produce less side effects because of the different pharmacodynamics of its metabolite norketamine.[8 9] However, a study of 100 children undergoing oral surgical procedures reported hallucinations in 20% of patients with ketamine 5 mg kg^{-1}–midazolam 0.35 mg kg^{-1}.[28] This high incidence may be a result of an unfortunate combination of doses. However, it is surprising that studies using only ketamine found no such problem. We tried to address the issue of psychedelic side effects with two structured interviews. The ketamine group had a slightly higher incidence of restless sleep and nightmares, but midazolam and the combination were equally well tolerated, as judged by our simple questions. In contrast, the incidence of vertigo and vomiting in children premedicated with ketamine alone precludes the further use of this regimen in our institution.

In summary, the results of our randomized, double-blind study confirm the basic findings of previous work which indicate that adding a low dose of ketamine to oral midazolam increases the success of premedication to greater than 90% without increasing side effects or prolonging recovery. The lower degree of sedation in our study is no disadvantage as long as successful separation and venepuncture coincide with good anxiolysis. Side effects were low and similar to midazolam alone.

References

1 Meursing AEE. Psychological effects of anesthesia in children. *Curr Opin Anesthesiol* 1989; **2**: 335–8

2 Geldner G, Hubmann M, Knoll R, Jacobi K. Comparison between three transmucosal routes of administration of midazolam in children. *Paediatr Anaesth* 1997; **7**: 103–9

3 McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth* 1992; **39**: 545–50

4 Haas U, Motsch J, Schreckenberger R, Bardenheuer HJ, Martin E. Prämedikation und präoperative Nahrungskarenz in der Kinderanästhesie. Ergebnisse einer Umfrage. *Anaesthetist* 1998; **47**: 838–43

5 Kain ZN, Mayes LC, Bell C, Weisman S, Hofstadter MB, Rimar S. Premedication in the United States: A status report. *Anesth Analg* 1997; **84**: 427–32

6 Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric premedicant. *Paediatr Anaesth* 1995; **5**: 293–5

7 Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. *Anesthesiology* 1990; **73**: 831–4

8 Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effect of i.m. and oral ketamine. *Br J Anaesth* 1981; **53**: 805–9

9 Gutstein HB, Johnson KL, Heard MB, Gregory GA. Oral ketamine preanesthetic medication in children. *Anesthesiology* 1992; **76**: 28–33

10 Cioaca R, Canavea I. Oral transmucosal ketamine: an effective premedication in children. *Paediatr Anaesth* 1996; **6**: 361–5

11 Sekerci S, Doenmez A, Ates Y, Oekten F. Oral ketamine in children (placebo controlled double-blind study). *Eur J Anaesthesiol* 1996; **13**: 606–11

12 Bowdle TA, Radant AD, Cowley DS, Kharash ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. *Anesthesiology* 1998; **88**: 82–8

13 Gingrich BK. Difficulties encountered in a comparative study of orally administered midazolam and ketamine. *Anesthesiology* 1994; **80**: 1414

14 Beebe DS, Belani KG, Chang PN, *et al.* Effectiveness of preoperative sedation with rectal midazolam, ketamine, or their combination in young children. *Anesth Analg* 1992; **75**: 880–4

15 Mitchell V, Grange C, Black A, Train J. A comparison of midazolam with trimeprazine as an oral premedicant for children. *Anaesthesia* 1997; **52**. 416–21

16 Bevan JC, Veall GRO, Macnab AJ, Ries CR, Marsland C. Midazolam premedication delays recovery after propofol without modifying involuntary movements. *Anesth Analg* 1997; **85**: 50–4

17 Alderson PJ, Lerman J. Oral premedication or paediatric ambulatory anaesthesia: a comparison of midazolam and ketamine. *Can J Anaesth* 1994; **41**: 221–6

18 Soliman IE, Patel RI, Ehrenpreis MB, Hanallah RS. Recovery scores do not correlate with postoperative hypoxemia in children. *Anesth Analg* 1988; **67**: 53–6

19 Lerman J. Study design in clinical research: sample size estimation and power analysis. *Can J Anaesth* 1996; **43**: 184–91

20 Lerman J. Sample size estimation for nominal data. *Can J Anaesth* 1997; **44**: 901

21 Altman DG. *Practical Statistics for Medical Research*. London: Chapman and Hall, 1991

22 Morgan-Hughes JO, Bangham JA. Pre-induction behaviour of children. A review of placebo-controlled trials of sedatives. *Anaesthesia* 1990; **45**: 427–35

23 Cray SH, Dixon JL, Heard CMB, Selsby DS. Oral midazolam premedication for paediatric day case patients. *Paediatr Anaesth* 1996; **6**: 265–70

24 Cetina J. Schonende Narkoseeinleitung bei Kindern durch orale oder rektale Ketamin-Dehydrobenzperidol-Applikation. *Anaesthesist* 1982; **31**: 277–9

25 Stewart KG, Rowbottom SJ, Aitken AW, Rajendram AS, Sudhaman DA. Oral ketamine premedication for paediatric cardiac surgery. *Anaesth Intensive Care* 1990; **18**: 11–14

26 Donahue PJ, Dineen PS. Emergence delirium following oral ketamine. *Anesthesiology* 1992; **77**: 604–5

27 Lin YC, Moynihan RJ, Hackel A. A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as preanesthetic medication for pediatric outpatients. *Anesthesiology* 1993; **70**: A1177

28 Roelofse JA, Louw LR, Roelofse PG. A double-blind randomized comparison of oral trimeprazine–methadone and ketamine–midazolam for sedation of pediatric dental patients for oral surgical procedures. *Anesth Prog* 1998; **45**: 3–11

British Journal of Anaesthesia **84** (3): 341–5 (2000)

S(+)-Ketamine for caudal block in paediatric anaesthesia†

P. Marhofer*, C. G. Krenn, W. Plöchl, T. Wallner, C. Glaser, H. Koinig, E. Fleischmann, A. Höchtl and M. Semsroth

Department of Anaesthesia and General Intensive Care, University of Vienna, Waehringer Guertel 18–20, A-1090 Vienna, Austria

**Corresponding author*

We have evaluated the intra- and postoperative analgesic efficacy of preservative-free S(+)-ketamine compared with bupivacaine for caudal block in paediatric hernia repair. After induction of general anaesthesia, 49 children undergoing hernia repair were given a caudal injection (0.75 ml kg^{-1}) of S(+)-ketamine 0.5 mg kg^{-1} (group K1), S(+)-ketamine 1.0 mg kg^{-1} (group K2) or 0.25% bupivacaine with epinephrine 1:200 000 (group B). No additional analgesic drugs were required during operation in any of the groups. Haemodynamic and respiratory variables remained stable during the observation period. Mean duration of analgesia was significantly longer in groups B and K2 compared with group K1 (300 (SD 96) min and 273 (123) min *vs* 203 (117) min; $P<0.05$). Groups B and K2 required less analgesics in the postoperative period compared with group K1 (30% and 33% *vs* 72%; $P<0.05$). Postoperative sedation scores were comparable between the three groups. We conclude that S(+)-ketamine 1.0 mg kg^{-1} for caudal block in children produced surgical and postoperative analgesia equivalent to that of bupivacaine.

Br J Anaesth 2000; **84**: 341–5

Keywords: anaesthetics local, bupivacaine; anaesthetics i.v., ketamine; pharmacokinetics, stereoisomers; anaesthetic techniques, regional, caudal; anaesthesia, paediatric

Accepted for publication: September 2, 1999

Caudal administration of bupivacaine is a widespread regional anaesthetic technique for intra- and postoperative analgesia during lower limb, anoperineal and abdominal surgical procedures in children.[1 2] Unintentional intravascular injection of bupivacaine during caudal block placement may cause life-threatening cardiovascular and central nervous system complications.[3–5] Even administration of an epidural test dose containing epinephrine for detection of unintentional intravascular cannula position does not reliably produce haemodynamic responses in children during inhalation anaesthesia.[6 7]

Naguib and colleagues[8] compared racemic ketamine with bupivacaine for caudal block in paediatric anaesthesia. While they observed adequate intra- and postoperative analgesia for racemic ketamine, this substance has not been adopted widely. Racemic ketamine is not recommended for epidural or spinal anaesthesia because of the neurotoxicity of the preservative agents that are contained in all commercially available ketamine preparations.[9]

S(+)-ketamine, one of two enantiomers of racemic ketamine, has three-fold the analgesic potency of racemic ketamine. Klimscha and colleagues[10] described the antinociceptive effects of S(+)-ketamine after intrathecal administration in rats and observed effective analgesia. Because S(+)-ketamine is available as a preservative-free drug, this substance has potential for epidural and intrathecal administration.

In this study, we have investigated the intra- and postoperative analgesic efficacy of two doses of caudally administered preservative-free S(+)-ketamine compared with bupivacaine during paediatric hernia repair.

Patients and methods

After obtaining approval from the Ethics Committee and informed parental consent, we studied 49 children (aged 3 months to 6 yr) in a prospective, randomized, double-blind study. Children were undergoing unilateral hernia repair and were allocated randomly to one of three groups for caudal block: 0.75 ml kg^{-1} injection of 0.25% bupivacaine with epinephrine 1:200 000 (group B); S(+)-ketamine 0.5 mg kg^{-1} (Ketanest S, Gödecke AG, Berlin, Germany) (group K1); or S(+)-ketamine 1.0 mg kg^{-1} (group K2). S(+)-ketamine was diluted in 0.9% saline. Drugs were prepared by a staff anaesthetist not otherwise involved in the study.

All children received midazolam 0.75 mg kg^{-1} rectally

---

†Presented in part at the ASA Annual Meeting, Orlando, October 17–21, 1998.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

as premedication, 20 min before operation. Intraoperative monitoring included electrocardiogram, heart rate (HR), pulse oximetry (Sp_{O_2}), mean arterial pressure (MAP) and end-tidal carbon dioxide concentration. Postoperative monitoring included HR, Sp_{O_2}, a pain/discomfort scale and a sedation score (see below). Before caudal block, i.v. access was established during sevoflurane anaesthesia administered via a face mask, and a glucose–saline solution 10 ml kg^{-1} was infused. Anaesthesia was maintained with 1.0–1.2% sevoflurane and 70% nitrous oxide in oxygen. Children breathed spontaneously via a laryngeal mask and, if necessary, with manual assistance to maintain an end-expired carbon dioxide partial pressure of 4.8–5.1 kPa[11] throughout the intraoperative period. No other anaesthetic was administered during operation. A glucose–saline solution was infused at a rate of 10 ml kg^{-1} h^{-1}.

Thereafter, caudal block was performed using a 22-gauge Quincke needle under aseptic conditions with the child in the left lateral position. The child was immediately turned supine after injection of the drug. MAP, HR and Sp_{O_2} values were obtained after induction of general anaesthesia, immediately after caudal injection and every 5 min thereafter during operation. Skin incision followed 15 min after caudal injection. At the beginning of skin closure, anaesthesia was discontinued. When patients were sufficiently awake, they were brought to the recovery room. After arrival, HR and Sp_{O_2} were noted every 15 min until 6 h after caudal block.

A decrease in MAP or HR of more than 30% from baseline during operation was defined as hypotension or bradycardia and treated with rapid infusion of fluids. If this was unsuccessful, etilefrine (an α- and β-sympathomimetic drug) in increments of 0.02 mg kg^{-1} or atropine 0.01 mg kg^{-1} was used, as appropriate. Respiratory depression was defined as a decrease in Sp_{O_2} of <93% that required supplementary oxygen via a face mask or laryngeal mask. An increase in HR or MAP of more than 10% during operation was defined as insufficient analgesia and treated with nalbuphine 0.2 mg kg^{-1} i.v.

The efficacy of postoperative analgesia was documented by an observational pain/discomfort scale (OPS) and by duration of analgesia after caudal block. We used the OPS to assess objective behavioural variables (crying, facial expression, position of the torso, position of legs, motor restlessness).[12] Each variable was scored on a three-point scale (1=none, 2=moderate, 3=severe) to give a cumulative score of 5–15. If the OPS score was >11 in two subsequent measurements, the patient was given paracetamol 30 mg kg^{-1}. Only data obtained before administration of paracetamol were included in the statistical analysis.

Duration of analgesia was defined as the time between caudal injection of drug and first rectal administration of paracetamol. If rectal administration of paracetamol was not necessary within the 6-h observation period, duration of analgesia was counted as 360 min. A four-point patient sedation score was assigned as follows: 1=asleep, not arousable by verbal contact; 2=asleep, arousable by verbal contact; 3=drowsy, not sleepy; 4=alert, awake. The patient sedation score was used to quantify sedation and to help identify possible systemic effects of ketamine. Patients were discharged from the recovery room to the ward 6 h after caudal injection. Postoperative measurements were performed by a staff anaesthetist not involved in the study.

Table 1 Patients characteristics (mean (SD or range)). Group B=0.25% bupivacaine with epinephrine 1:200 000, group K1=S(+)-ketamine 0.5 mg kg^{-1}, and group K2=S(+)-ketamine 1.0 mg kg^{-1}. No significant differences between groups

	Group B (*n*=17)	**Group K1** (*n*=14)	**Group K2** (*n*=18)
Age (months)	42 (3–72)	44 (7–72)	48 (20–72)
Weight (kg)	16 (6)	15 (5)	17 (5)
Height (cm)	99 (20)	97 (20)	103 (11)
Sex (F/M)	4/13	4/10	5/13
Duration of surgery (min)	40 (21)	37 (20)	37 (14)

Statistical analysis

Power analysis for duration of analgesia was calculated using data from a pilot study (δ=100, power=0.85, α=0.05). All data are presented as mean (SD) except where specified. All haemodynamic data were calculated and compared with baseline values within each study group, in addition to corresponding times between groups, using the Student's *t* test and one-way analysis of variance followed by a *post hoc* test (Scheffé). Evaluation of OPS, patient sedation score, duration of analgesia and time to first spontaneous voiding was accomplished using the Kruskal–Wallis *H* test and the Mann–Whitney *U* test, as appropriate. Proportional data were evaluated using the chi-square and Fisher exact tests. Probability values <0.05 were considered significant.

Results

We investigated 49 ASA I children in three study groups. The groups were comparable in age, weight, height, sex and duration of surgical procedure (Table 1). Additional analgesics during operation were not required in any child. All children were sufficiently awake within 10 min and were brought to the recovery room breathing room air. None of the children required treatment for hypotension or bradycardia.

We found no significant differences between groups B and K2 for duration of analgesia (300 (96) min and 273 (123) min) (Fig. 1) or additional postoperative analgesic requirements (Fig. 2). However, groups B and K2 were significantly different from group K1 for duration of analgesia (203 (117) min; $P<0.05$ *vs* groups B and K2) and additional postoperative analgesic requirements (Figs 1, 2). In groups B and K2, 30% and 33% of children, respectively, required additional analgesics. In group K1, 72% of children required additional analgesics ($P<0.05$ *vs* groups B and K2).

There was no significant change in HR or MAP during the intraoperative period in any group (Fig. 3). Respiratory

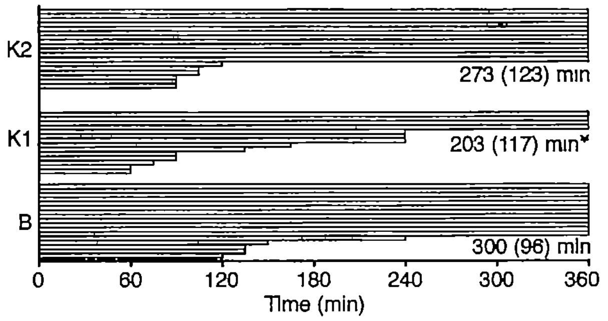


Fig 1 Duration of analgesia for every patient and average duration of analgesia (median (range)) during the 6-h observation period in the recovery room. Group B=0.25% bupivacaine with epinephrine 1:200 000; group K1=S(+)-ketamine 0.5 mg kg^{-1}; group K2=S(+)-ketamine 1.0 mg kg^{-1}. *Significant difference in mean duration of analgesia compared with groups K2 and B ($P<0.05$).

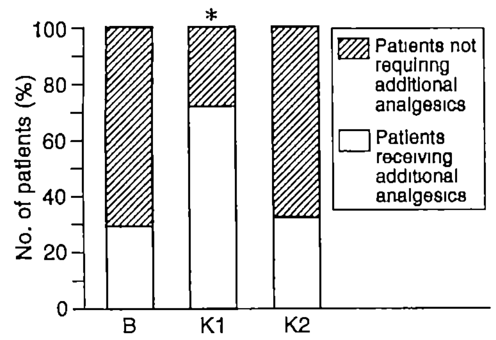


Fig 2 Analgesic requirements during the postoperative period in the recovery room. Group B=0.25% bupivacaine with epinephrine 1:200 000; group K1=S(+)-ketamine 0.5 mg kg^{-1}; group K2=S(+)-ketamine 1.0 mg kg^{-1}. *Significant difference compared with groups K2 and B ($P<0.05$).

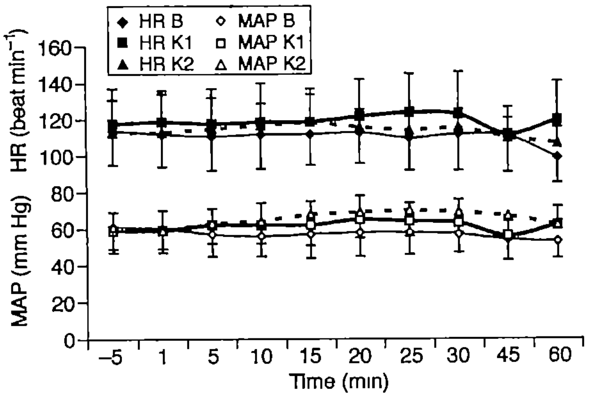


Fig 3 Haemodynamic changes (heart rate (HR) and mean arterial pressure (MAP)) after caudal injection and during the intraoperative period (mean (SD)). Group B=0.25% bupivacaine with epinephrine 1:200 000; group K1=S(+)-ketamine 0.5 mg kg^{-1}; group K2=S(+)-ketamine 1.0 mg kg^{-1}

depression was not observed, and Sp_{O_2} values during and after operation did not differ between groups. We found no significant difference in postoperative sedation scores (data not shown).

Time to first spontaneous voiding was 309 (95) min in group B, 297 (101) min in group K1 and 322 (87) min in group K2 (ns). Times to first standing were not measured, but we did not observe significant motor block, and all children moved their legs spontaneously when leaving the recovery room 6 h after caudal injection.

Discussion

Ours is the first study to investigate the use of S(+)-ketamine for caudal block in children. Our results indicated that preservative-free S(+)-ketamine 1.0 mg kg^{-1} provided equipotent intra- and postoperative analgesia compared with 0.25% bupivacaine with epinephrine 1:200 000. S(+)-ketamine 0.5 mg kg^{-1} provided equipotent analgesia compared with 0.25% bupivacaine–epinephrine 1:200 000 only in the intraoperative period.

Caudal anaesthesia in combination with general inhaled anaesthesia is used widely for many surgical procedures in children.[1 2] Although we did not study i.v. administration of bupivacaine, unintentional i.v. administration of local anaesthetic, resulting in severe cardiovascular and central nervous system complications, has been described in the literature.[3–5] As S(+)-ketamine 1.0 mg kg^{-1} is the recommended dose for i.v. administration, unintentional i.v. administration during caudal injection would be harmless, and the analgesic effect would be systemic.

Ketamine, a derivative of phencyclidine, has a chemical structure similar to that of bupivacaine and therefore has local anaesthetic effects.[13 14] These local anaesthetic effects are also caused by *N*-methyl-D-aspartate receptor antagonism (NMDA receptors are in the substantia gelatinosa in the spinal cord), opioid μ receptor agonism and voltage-sensitive sodium channel interaction.[15–19] Previous studies have investigated racemic ketamine for epidural administration in adult patients. While some authors observed sufficient analgesic effects of peridurally administered racemic ketamine,[20–23] others did not.[24–26] Racemic ketamine for caudal block in children has been found to be comparable with bupivacaine.[8 27] Nevertheless, racemic ketamine is not recommended for epidural or intrathecal administration because of possible neurotoxic effects of the preservatives benzethonium chloride and chlorbutanol.[28 29] Only Semple and colleagues[27] used preservative-free racemic ketamine for caudal block in children in combination with bupivacaine. Therefore, definitive evidence of the analgesic potency of racemic ketamine from that study is not possible. Furthermore, preservative-free racemic ketamine is not available commercially.

S(+)-ketamine, the (+)-enantiomer of racemic ketamine, has three times the analgesic potency of the racemate.[30] The pharmacological properties[30] and haemodynamic responses[31] are comparable with those of the racemic compound. Klimscha and colleagues[10] investigated the antinociceptive effect of S(+)-ketamine and described an analgesic potency of S(+)-ketamine sufficient for treating inflammatory pain in rats. The clinical use of S(+)-ketamine in regional anaesthesia has never been described, but NMDA antagonism,[17] μ receptor agonism,[18] the voltage-sensitive sodium channel interaction[19] and the commercial availability of the preservative-free formulation makes it a potential substance for caudal administration.

We observed adequate intraoperative effects of S(+)-ketamine 0.5 and 1.0 mg kg^{-1} for caudal block in children. Haemodynamic responses after caudal administration of S(+)-ketamine were comparable with those after caudal administration of bupivacaine. We did not observe increases in HR or MAP after administration of S(+) ketamine. This indicates that the analgesic effect of caudally administered S(+)-ketamine is caused primarily by a direct effect on the spinal cord with little systemic effects. This corresponds to the results of Dhasmana and colleagues.[32] In that study, intrathecally administered ketamine caused a decrease in arterial pressure whereas administration of ketamine into the carotid artery was followed by an immediate increase in arterial pressure and heart rate. Dhasmana and colleagues interpreted these results as a direct effect of intrathecally administered ketamine on the spinal cord. The spinal analgesic mechanism has also been described by Hanaoka and colleagues.[33] They showed that the analgesic effect of racemic ketamine on the spinal cord can be antagonized by naloxone in cats.

Caudally administered S(+)-ketamine 1.0 mg kg^{-1} provided equipotent postoperative analgesic effects to bupivacaine. The fact that postoperative sedation scores were comparable between groups also indicates the non-systemic analgesic effect of caudally administered S(+)-ketamine. Nevertheless, we did not observe the children after they were discharged from the recovery room, 6 h after caudal injection. Therefore, we cannot draw any conclusions on the exact analgesic duration of caudally administered S(+)-ketamine. However, all children discharged from the recovery room moved their legs spontaneously and were awake.

Acknowledgement

We thank Gerold Reimitzer from Godecke Ltd, Austria, for providing preservative-free S(+)-ketamine (Ketanest S; Parke Davis) and patients' medical insurance.

References

1 Dalens B, Hasnaoui A. Caudal anesthesia in pediatric surgery: success rate and adverse effects in 750 consecutive patients. *Anesth Analg* 1989; **68**: 83–9

2 Yaster M, Maxwell LG. Pediatric regional anesthesia. *Anesthesiology* 1989; **70**: 324–38

3 Freid EB, Bailey AG, Valley RD. Electrocardiographic and hemodynamic changes associated with unintentional intravascular injection of bupivacaine with epinephrine in infants. *Anesthesiology* 1993; **79**: 394–8

4 Ved SA, Pinosky M, Nicodemus H. Ventricular tachycardia and brief cardiovascular collapse in two infants after caudal anesthesia using a bupivacaine–epinephrine solution. *Anesthesiology* 1993; **79**: 1121–3

5 Prentiss JE. Cardiac arrest following caudal anesthesia. *Anesthesiology* 1979; **50**: 51–3

6 Kozek-Langecker S, Marhofer P, Krenn CG, et *al.* Simulation of an epidural test dose with intravenous epinephrine under halothane and sevofluran narcosis. *Acta Chir Aust* 1998; **139**: 22

7 Desparmet J, Mateo J, Ecoffey C, Mazoit X. Efficacy of an epidural test dose in children anesthetized with halothane. *Anesthesiology* 1990; **72**: 249–51

8 Naguib M, Sharif AY, Seraj M, El Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: Comparison with caudal bupivacaine. *Br J Anaesth* 1991; **67**: 559–64

9 Gebhardt B. Epidural and intrathecal administration of ketamine—pharmacology and clinical results. *Anaesthesist* 1994; **43**: S34-40

10 Klimscha W, Horváth G, Szikszay M, Bobos I, Benedek G. Antinociceptive effects of the S-(+) enantiomer of ketamine on carrageenan hyperalgesia after intrathecal administration in rats. *Anesth Analg* 1998; **86**: 561–5

11 Jöhr M. *Kinderanästhesie*, 4 Edn. Lübeck, Germany: Gustav Fischer Verlag, 1998; 121–2

12 Buttner W, Breitkopf L, Miele B, Finke W. Initial results of the reliability and validity of a German-language scale for the quantitative measurement of postoperative pain in young children. *Anaesthesist* 1990; **39**: 593–602

13 Dowdy EG, Kaya K, Gocho Y. Some pharmacologic similarities of ketamine, lidocaine, and prilocaine. *Anesth Analg* 1973; **52**: 839–42

14 Brau M, Sander F, Vogel W, Hempermann G. Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. *Anesthesiology* 1997; **86**: 394–404

15 Smith DJ, Bouchal RL, deSactis CA. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 1987; **26**: 1253–60

16 Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. *Br J Anaesth* 1996; **77**: 441–4

17 Martin D, Lodge D. Ketamine acts as a non-competitive N-methyl-D-aspartate antagonist on frog intrathecal cord in vitro. *Neuropharmacology* 1985; **24**: 999–1003

18 Ahuja BR. Analgesic effect of intrathecal ketamine in cats. *Br J Anaesth* 1983; **55**: 991–5

19 Brau M, Sander F, Vogel W, Hempelmann G. Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. *Anesthesiology* 1997; **86**: 394–404

20 Islas JA, Astorga J, Laredo M. Epidural ketamine for control of postoperative pain. *Anesth Analg* 1985; **64**: 1161–2

21 Saissy JM, Drissi-Kamili N, Noureddine A, Mabrouk H. Contribution à l'étude de l'analgésie post-opératoire à la kétamine par voie péridurale. *Conv Méd* 1984; **3**: 5–7

22 Saissy JM. Analgésie post-opératoire par administration péridurale continue de kétamine. *Ann Fr Anesth Reanim* 1985; **4**: 390–1

23 El-Khateeb OE, Ragab A, Metwalli M, Hassan HA. Assessment of epidural ketamine for relief of pain following vaginal and lower abdominal surgery. In: Domino EF, ed. *Status of Ketamine in Anesthesiology*. Ann Arbor: NPP Books, 1980; 403–9

24 Kawana Y, Sato H, Shimada H, *et al.* Epidural ketamine for postoperative pain relief after gynecologic operations. *Anesth Analg* 1987; **66**: 735–8

25 Ravat F, Dorne R, Baechle JP, *et al.* Epidural ketamine or morphine for postoperative analgesia. *Anesthesiology* 1987; **66**: 819–22

26 Naguib M, Adu-gyamfi Y, Absood GH, Farag H, Gyasi HK. Epidural

ketamine for postoperative analgesia. *Can Anaesth Soc J* 1986; **33**: 16–21

27 Semple D, Findlow D, Aldridge LM, Doyle E The optimal dose of ketamine for caudal epidural blockade in children. *Anaesthesia* 1996; **51**: 1170–2

28 Malinovsky JM, Lepage JY, Mussini JM, Pinaudt M, Souron R. Is ketamine or its preservative responsible for neurotoxicity in the rabbit? *Anesthesiology* 1993; **78**. 109–15

29 Migaly P. The problem of intrathecal ketamine. *Br J Anaesth* 1986; **58**: 684

30 Adams HA, Werner C. (S)-ketamine—renaissance of a substance? *Anaesthesist* 1997; **46**. 1046–2

31 Geisslinger G, Hering W, Thomann P, *et al.* Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytic method. *Br J Anaesth* 1993; **70**. 666–71

32 Dhasmana KM, Salt PJ, Faithfull NS, Erdmann W. Effect of intrathecal and intracarotid administration of ketamine on blood pressure and heart rate in rats. *Arch Int Pharmacodyn Ther* 1986; **280**: 97–105

33 Hanaoka K, Tagami M, Nagase M, Ide Y, Yamamura H. Spinal analgesic mechanisms of ketamine. antagonism by naloxone. In: Domino EF, ed. *Status of Ketamine in Anesthesiology* Ann Arbor: NPP Books, 1980; 229–38

British Journal of Anaesthesia **84** (3): 346–9 (2000)

Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration

B. V. S. Murthy[1], K. S. Pandya[1], P. D. Booker*, A. Murray, W. Lintz[2] and R. Terlinden[2]

Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP, UK
**Corresponding author*
Present addresses: [1]Department of Anaesthesia, Royal Liverpool University Hospital, Prescot Street, Liverpool, UK.
[2]Department of Pharmacokinetics, Grünenthal GmbH Research Centre, Aachen, Germany

We have studied the pharmacokinetics of a single bolus dose of tramadol 2 mg kg^{-1} injected either i.v. or into the caudal epidural space in 14 healthy children, aged 1–12 yr, undergoing elective limb, urogenital or thoracic surgery. Serum concentrations of tramadol and its metabolite O-demethyl tramadol (M1) were measured in venous blood samples at various intervals up to 20 h by non-stereoselective gas chromatography with nitrogen-selective detection. All pharmacokinetic variables were evaluated using a non-compartmental model. After a single i.v. injection (n=9), the mean elimination half-life of tramadol was 6.4 (SD 2.7) h, with a volume of distribution of 3.1 (1.1) litre kg^{-1} and total plasma clearance of 6.1 (2.5) ml kg^{-1} min^{-1}. All of these pharmacokinetic variables were similar to those reported previously in adults. After caudal epidural administration (n=5), mean elimination half-life was 3.7 (0.9) h, volume of distribution was 2.0 (0.4) litre kg^{-1} and total clearance was 6.6 (1.9) ml kg^{-1} min^{-1}. The caudal/i.v. quotient of the AUC was 0.83, which confirms that there is extensive systemic absorption of tramadol after caudal administration. Serum concentrations of M1 showed a time course typical of a metabolite after both modes of administration. Serum concentrations of M1 after caudal administration were lower than those after i.v. injection.

Br J Anaesth 2000; **84**: 346–9

Keywords: analgesics opioid, tramadol; pharmacokinetics, tramadol; analgesia, paediatric; children; analgesic techniques, i.v.; analgesic techniques, epidural

Accepted for publication: September 6, 1999

Tramadol is a centrally acting analgesic which has been licensed for use in children older than 12 yr in the UK since 1994, although it has been licensed in children older than 1 yr of age in many other European countries since 1977. It acts at opioid receptors and also appears to modify transmission of pain impulses by inhibition of monoamine reuptake.[1] Tramadol is a racemic mixture of two enantiomers. The (+)-enantiomer has a moderate affinity for the opioid μ receptor, greater than that of the (–)-enantiomer. In addition, the (+)-enantiomer inhibits serotonin reuptake and the (–)-enantiomer is a norepinephrine reuptake inhibitor. These complementary properties result in a synergistic antinociceptive interaction between the two enantiomers.[1] The result is an opioid with a striking lack of respiratory depressant effect despite an analgesic potency approximately equal to that of pethidine.[2–4] Furthermore, animal work has suggested that tramadol may have a selective spinal action.[5] Tramadol has been shown to provide effective, long-lasting analgesia after epidural administration in both adults[6 7] and children.[8 9] In addition, biotransformation of tramadol in the liver results in many phase I and II metabolites. Of all the metabolites, O-demethyl tramadol (M1) is the only active metabolite[10] with a greater affinity for the μ receptor than the parent compound.[11]

Although the pharmacokinetics of tramadol in adults after i.v. and enteral administration have been studied,[12 13] there are no comparative data in children. Therefore, we have investigated the pharmacokinetics of a single bolus dose of tramadol 2 mg kg^{-1} injected either i.v. or into the caudal epidural space in children.

Patients and methods

After obtaining approval from the Local Ethics committee and written, informed parental consent, we studied 14 healthy children, ASA I and II, aged 1–12 yr, undergoing elective surgery. Nine children requiring limb and thoracic surgery were given a single i.v. injection of tramadol and five children requiring urogenital surgery were given a single injection of tramadol into the caudal epidural space. Children were excluded if they were undergoing day-case surgery or were receiving concurrent medications.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

No premedication was given. EMLA cream (Astra UK Ltd) was applied over two visible veins 1–1.5 h before surgery. On arrival in the anaesthetic room, i.v. cannulation was performed and anaesthesia was induced with thiopental 5 mg kg^{-1}. In four patients, neuromuscular block was achieved with atracurium 0.5 mg kg^{-1} for facilitation of tracheal intubation, while in other children (n=10) a laryngeal mask airway was inserted. Anaesthesia was maintained with an end-tidal isoflurane concentration of 0.5–1% and 66% nitrous oxide in oxygen. A second large i.v. cannula (20-gauge) was inserted into a long saphenous vein at the ankle to facilitate subsequent blood sampling. Before surgery, i.v. injection of tramadol (Zydol, Searle UK Ltd) 2 mg kg^{-1} diluted in 0.9% saline 10 ml was given over 30 s via the cannula in the hand to those children undergoing limb or thoracic surgery (n=9). For those children undergoing hypospadias repair (n=5), an injection of tramadol 2 mg kg^{-1}, diluted with 0.9% saline to a total volume of 0.75 ml kg^{-1}, was given into the caudal epidural space. During and after operation, rescue analgesia was provided using i.v. morphine, rectal diclofenac or oral paracetamol, as indicated clinically.

For subsequent evaluation of serum concentrations of tramadol and its metabolite M1, 2-ml blood samples were obtained from the indwelling venous cannula at regular time intervals after injection of drug. In the i.v. group, blood samples were obtained at 10, 20, 30, 45 and 60 min and at 2, 3, 4, 6, 8, 10, 12, 16 and 20 h after injection. In the caudal group, blood samples were obtained at 15, 30, 45 and 60 min and at 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 20 h after injection of tramadol. The samples were centrifuged, the serum separated and stored at –20°C until assay. Serum concentrations of tramadol and its metabolite M1 were measured simultaneously by non-stereoselective gas chromatography with nitrogen-selective detection.[14] Diazoethane was used as the derivatization agent for M1. The calibration curves with sample concentrations of 2.5–500 ng ml^{-1} for tramadol and 2–200 ng ml^{-1} for M1 were linear, with a coefficient of correlation greater than 0.997. The precision and accuracy of the assay were high with a coefficient of variation of 4.2–8.4% for tramadol and 2.9–8.4% for M1. Checks were made to ensure that lidocaine, thiopental, morphine, diclofenac and paracetamol did not interfere with the non-stereoselective assay method.

The pharmacokinetic evaluation was performed using the model-independent method, with the software program MODINDEP developed by the Department of Pharmacokinetics of Grunenthal GmbH and validated with the non-compartmental part of TOPFIT 2.0.[15] Peak serum concentrations (C_{P}max), time to peak concentrations (tC_{P}max) and area under the serum concentration curve (AUC) were derived from individual concentration–time courses. The elimination half-life ($T_{1/2}{}^{\beta}$), total clearance (Cl_{tot}), volume of distribution (Vd^{β}) and mean residence time (MRT) were calculated using standard formulae.[16]

All values are expressed as mean (SD). Patient characteristics in both groups were compared using an unpaired t test (SPSS, UK Ltd). A probability of <5% was considered statistically significant.

Results

Patient characteristics and pharmacokinetic variables for those who received i.v. and caudal tramadol are shown in Table 1. The median age of children in the i.v. group was 2.42 (range 1.17–6.58) yr, which was significantly different from that in the caudal group (median age 6.0 (5.5–12) yr).

Tramadol

After i.v. injection, the serum concentration decay curve followed a biexponential pattern with a highest mean concentration of 1079 (SD 442) ng ml^{-1} at 0.19 (0.06) h (Fig. 1). After caudal administration, the time course of mean serum tramadol concentrations was characterized by a peak of 709 (259) ng ml^{-1} at 0.5 (0.11) h (Fig. 1). At 4 h after i.v. injection, mean serum concentration was 369 (133) ng ml^{-1}, whereas a mean concentration of 411 (106) ng ml^{-1} was obtained after caudal administration.

O-demethyl tramadol (M1)

After i.v. injection, the metabolite M1 had a mean peak serum concentration of 63.9 (30.7) ng ml^{-1} at 4.9 (1.9) h

Table 1 Patient characteristics and pharmacokinetics variables (mean (SD or range)) of tramadol and its metabolite M1 after a bolus dose of tramadol 2 mg kg^{-1} injected either i.v. (n=9) or caudally (n=5) $^{*}P<0.05$

	Tramadol		**M1**	
	I.v.	**Caudal**	**I.v.**	**Caudal**
Age (yr)	3.07 (1.17–6.58)*	8.2 (5.5–12.0)	–	–
Weight (kg)	13.3 (5.2)*	24.4 (8.0)	–	–
C_{P}max (ng ml^{-1})	1079 (442)	709 (259)	63.9 (30.7)	40.3 (4.3)
tC_{P}max (h)	0.19 (0.06)	0.55 (0.11)	4.9 (1.9)	6.4 (1.5)
AUC (h ng ml^{-1})	5738 (2794)	4774 (1581)	1172 (597)	556 (129)
$T_{1/2}{}^{\beta}$ (h)	6.4 (2.7)	3.7 (0.9)	10.6 (8.5)	5.4 (2.0)
Cl_{tot} (ml kg^{-1}min^{-1})	6.1 (2.5)	6.6 (1.9)	–	–
Vd^{β} (litre kg^{-1})	3.1 (1.1)	2.0 (0.4)	–	–
MRT (h)	8.5 (3.7)	6.5 (1.3)	17.6 (12.4)	10.8 (2.9)

(Fig. 2). After caudal administration, the peak value (40.3 (4.3) ng ml^{-1}) of M1 was observed at 6.4 (1.5) h (Fig. 2).

Discussion

We found that mean serum concentrations of tramadol and its metabolite M1 after a single i.v. injection of tramadol were only slightly higher than those in adults.[12] Similarly, none of the pharmacokinetic variables calculated was significantly different from those reported previously in healthy adults.[12] In our study, tramadol had a mean Vd^{β} of 3.1 (1.1) litre kg^{-1}, which agrees with a value of 2.74 (0.54) litre kg^{-1} in adults.[12] Mean elimination half-life was 6.4 (2.7) h and mean total plasma clearance 6.1 (2.5) ml min^{-1} kg^{-1}, which are comparable with values of 5.1 (0.8) h and 6.31 (1.68) ml min^{-1} kg^{-1}, respectively, in healthy adult volunteers.[12 13] Thus our results give no indication of any clinically significant difference in the pharmacokinetics of tramadol between children (1–12 yr) and adults after i.v. injection. It would appear, therefore, that on the basis of the pharmacokinetic data available at present, children require the same body weight related doses as adults. We cannot compare our results from children given a caudal epidural injection of tramadol with those in adults, as no pertinent data are available.

Although tramadol is a racemic mixture of two enantiomers,[1] stereoselective analytical methods in adults have demonstrated that the pharmacokinetic differences between the enantiomers of tramadol and its metabolite are of minor significance.[17] In addition, the inter-individual variability of (+)-tramadol/total tramadol and (+)-M1/total M1 ratios are low (cv <5%) (data on file at Grunenthal GmbH). Moreover, pilot experiments using stereoselective analytical methods have shown that the same is true for the pharmacokinetics of tramadol and M1 in children (data on file at Grunenthal GmbH). Hence application of a non-selective analytical method in the present study was justified.

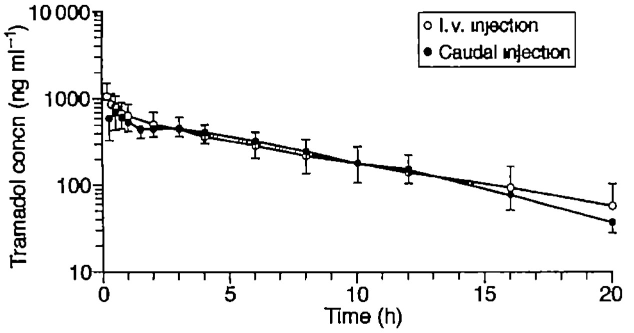


Fig 1 Mean (SD) serum concentrations of total tramadol after i.v. or caudal injection of tramadol 2 mg kg^{-1}.

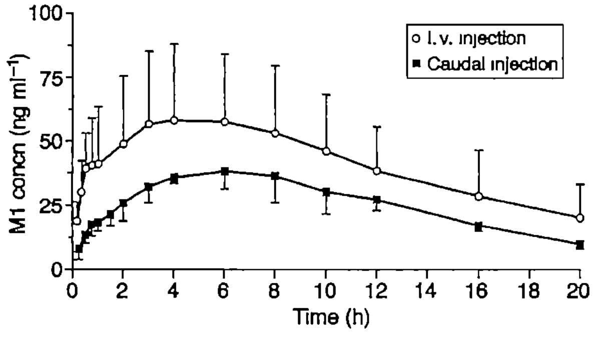


Fig 2 Mean (SD) serum concentrations of O-demethyl tramadol (M1) after i.v. or caudal injection of tramadol 2 mg kg^{-1}.

In view of the differences in age and weight, it may be that they were different populations. In addition, the two different anaesthetic techniques would have affected blood flow to the various compartments and some of the pharmacokinetic data. Hence comparison of the two groups is not possible. In our study, peak serum concentrations of tramadol were observed at 0.55 (0.11) h after caudal administration whereas maximum serum concentrations after i.m. injection in healthy adults occurred at 0.75 (0.38) h.[18] These data would suggest that there is more rapid transfer of tramadol to the systemic circulation after caudal administration than after i.m. administration. Moreover, in our study, the mean AUC after caudal administration was only 17% lower than that after i.v. injection, confirming that there is extensive systemic absorption of tramadol after caudal administration. An exact value for the extent of systemic bioavailability after epidural administration cannot be determined because the data for the two modes of administration were obtained from two different subject groups. Hence analgesia that is produced after epidural injection may be attributable to systemic availability alone. The significant delay in onset time for analgesic effect after caudal administration, demonstrated in clinical studies,[8] is in accordance with the fact that peak serum concentrations are reached significantly later after caudal epidural than after i.v. injection. We hypothesize that tramadol, injected into the epidural space, has a prolonged duration of action because of sustained release of drug from epidural fat and other relatively poorly perfused tissues.

Recently published results suggest that the metabolite M1 has a $T_{1/2}{}^{\beta}$ of 6–7 h in healthy adult volunteers[13] and contributes to the analgesic effect of the parent drug.[19] As O-demethylation of tramadol is carried out by cytochrome P-450 systems[20] and P-450 activity has usually reached adult levels by 1 yr of age,[21 22] it is not surprising that the M1/tramadol serum concentration ratio after i.v. injection we found in children was similar to that reported previously in adults.[13]

In summary, we believe that there is no logical reason to inject tramadol into the epidural space. Injection of tramadol into the epidural space appears to act only as a depot for immediate and delayed systemic absorption. Administration by other enteral and parenteral routes is equally efficacious and long lasting, particularly if repeated doses are given. We believe that further pharmacokinetic studies of tramadol in children examining blood concentrations after repeat i.v. or oral administration would be justified.

References

1 Raffa RB, Friderichs E, Reimann W, et *al.* Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. *J Pharmacol Exp Ther* 1993; **267**: 331–40

2 O'Flaherty D, Szekely S, Vickers MD. Tramadol versus pethidine analgesia in postoperative pain. *Pain* 1990; **5**. S179

3 Lehmann KA, Jung C, Hoekle W. Tramadol and pethidine in postoperative pain therapy: a randomized double-blind trial with intravenous on-demand analgesia. *Schmerz Pain Douleur* 1985; **6**: 88–100

4 Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration *Anaesthesia* 1992; **47**: 291–6

5 Mattia A, Vanderah T, Raffa RB, Vaught JL, Porreca P. Tramadol produces antinociception through spinal sites, with minimal tolerance, in mice. *FASEB J* 1991; **5**: A473

6 Baraka A, Jabbour S, Ghabash M, Nader A, Khoury G, Sibai A. A comparison of epidural tramadol and epidural morphine for postoperative analgesia *Can J Anaesth* 1993; **40**: 308–13

7 Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. *Anaesthesia* 1993; **48**: 328–31

8 Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. *Br J Anaesth* 1997; **79**: 293–6

9 Torres LM, Almarcha JM, Calderón E, De Antonio P, López-Fernández J, Pérez-Pérez A. Analgesia caudal postoperatoria en pediatría. Bupivacaína vs tramadol. *Rev Soc Esp del Dolor* 1995; **2**: 237–41

10 Lintz W, Erlacin S, Frankus E, Uragg H. Biotransformation of tramadol in man and animal. *Arzneim -Forsch /Drug Res* 1981; **31**: 1932–43

11 Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selective opioids *Arzneim -Forsch /Drug Res* 1988; **38**: 877–80

12 Lintz W, Barth H, Osterloh G, Schmidt-Bothelt E. Bioavailability of enteral tramadol formulations. *Arzneimittelforschung* 1986; **36**. 1278–83

13 Liao S, Hill JF, Nayak RK. Pharmacokinetics of tramadol following single and multiple oral doses in man. *Pharm Res* 1992; **9**. 308

14 Becker R, Lintz W Determination of tramadol in human serum by capillary gas chromatography with nitrogen-selective detection. *J Chromatogr* 1986; **377** 213–20

15 Heinzel G, Woloszczak R, Thomann P *TopFit 2.0 Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC.* Stuttgart: Gustav Fischer Verlag, 1993

16 Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. *J Pharmacokinet Biopharm* 1976; **4**: 443–67

17 Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. *Clin Pharmacokinet* 1999, **37**. 17–40

18 Lintz W, Beier H, Gerloff J. Bioavailability of tramadol after i.m. injection in comparison to i v infusion. *Int J Clin Pharmacol Ther* 1999; **37**: 175–83

19 Poulsen L, Arendt-Nielsen L, Brosen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther* 1996; **60**. 636–44

20 Paar WD, Frankus P, Dengler HJ. The metabolism of tramadol by human liver microsomes. *Clin Invest* 1992; **70**: 708–10

21 Leeder JS, Kearns GL. Pharmacogenetics in pediatrics. Implications for practice. *Pediatr Clin North Am* 1997, **44**: 55–77

22 Kearns GL, Reed MD. Clinical pharmacokinetics in infants and children. A reappraisal. *Clin Pharmacokinet* 1989; **17**: 29–67

British Journal of Anaesthesia 84 (3): 350–3 (2000)

Comparison of compound A concentrations with sevoflurane anaesthesia using a closed system with a PhysioFlex anaesthesia machine *vs* a low-flow system with a conventional anaesthesia machine

H. Bito*, A. Suzuki, Y. Sanjo, T. Katoh and S. Sato

Department of Anesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu 431-3192, Japan

**Corresponding author*

Sevoflurane anaesthesia was conducted using a totally closed circuit PhysioFlex anaesthesia machine (PhysioFlex group) or with a standard Modulus CD anaesthesia machine (Modulus group) ($n=8$ in each group). The PhysioFlex was used under closed system conditions and the Modulus was used under low-flow system conditions (flow rate 1 litre min^{-1}). Concentrations of sevoflurane degradation products and the temperature of soda lime were compared. Degradation products in the circuit were measured hourly, and the temperature of soda lime was monitored. The only degradation product detected was $CF_2=C(CF_3)\text{-O-}CH_2F$ (compound A). Maximum concentrations of compound A were significantly lower (median 8.5 (range 5.4–15.9) ppm) in the PhysioFlex than in the Modulus group (21.2 (16.5–27.4) ppm) ($P<0.05$). The maximum temperature of soda lime was also significantly lower in the PhysioFlex group (35.3 (32.1–36.3)°C vs 44.6 (43.0–47.1)°C, respectively) ($P<0.05$). Hourly compound A concentrations were lower in the PhysioFlex group than in the Modulus group. End-tidal sevoflurane concentrations during measurement of degradation products were not different between groups. Therefore, use of the totally closed PhysioFlex system may significantly reduce compound A concentrations compared with low-flow anaesthesia using a standard anaesthesia machine.

Br J Anaesth 2000; **84**: 350–3

Keywords: equipment, anaesthesia machines; anaesthetics volatile, sevoflurane

Accepted for publication: September 23, 1999

Sevoflurane reacts with soda lime, resulting in generation of several degradation products.[1] Five degradation products of sevoflurane have been identified *in vitro*,[2] one of which $CF_2=C(CF_3)\text{-O-}CH_2F$ (compound A), has been reported to be nephrotoxic in rats.[3–6]

The PhysioFlex anaesthesia machine was designed specifically to deliver anaesthetics in a closed system.[7–11] Several studies have examined concentrations of sevoflurane degradation products under both closed and low-flow systems,[12–17] but none to date has examined closed system conditions with the PhysioFlex. Wissing, Kuhn and Kessler reported that under closed system conditions, the canister temperatures in the PhysioFlex were lower than those in a standard anaesthesia machine.[11] This led us to predict that the concentration of compound A in a circle system would be lower in the PhysioFlex than in a standard anaesthesia machine under closed system conditions because higher temperatures of soda lime produce higher compound A concentrations.[16–18]

Therefore, in this study, we have measured compound A concentrations in the circle system and the temperature of soda lime in the PhysioFlex under closed system conditions and compared these results with those from a standard anaesthesia machine under low-flow conditions.

Patients and methods

The study was approved by our institution's Committee on Human Research, and informed consent was obtained from all patients. The study group comprised 16 patients, ASA I or II, undergoing general anaesthesia of 3–4 h duration. Patients were allocated randomly to one of two groups. A PhysioFlex anaesthesia machine (Drager, Lubeck, Germany) was used in eight patients (PhysioFlex group) and the Modulus CD Anaesthesia System (Ohmeda, Madison, WI, USA) was used in the other eight patients (Modulus group).

Premedication consisted of hydroxyzine 50 mg and atropine 0.5 mg i.m., given 45 min before induction of anaesthesia. After preoxygenation, anaesthesia was induced with thiopental 4–5 mg kg^{-1}, and vecuronium 0.12–

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

0.15 mg kg^{-1} was given. After tracheal intubation, patients in the PhysioFlex group were connected to the PhysioFlex with an inspired oxygen concentration of 35% in nitrous oxide. In the Modulus group, the total flow rate for maintenance of anaesthesia was 1 litre min^{-1}, and the ratio of oxygen and nitrous oxide flow rates was controlled so that the oxygen concentration in the inspiratory limb was greater than 35%. In both groups, sevoflurane concentration was regulated so that systolic arterial pressure was maintained within ±20% of baseline values. Respiration was controlled by a respirator so that tidal volume was 10–12 ml kg^{-1}, and ventilatory frequency was adjusted to maintain end-tidal carbon dioxide concentration at 4.0–5.3 kPa.

Soda lime (Sodasorb II, W.R. Grace and Co., Lexington, MA, USA) was used as the carbon dioxide absorbent, and was replaced with fresh absorbent before the start of each case. Temperature was monitored at the centre of the canister in the PhysioFlex group and at the centre of the upper compartment of the canister in the Modulus group.

Sample gas for measurement of degradation products was collected from the inspiratory limb of the anaesthesia circuit. The constant end-tidal sevoflurane concentration was maintained for at least 10 min before sampling of the circuit. Concentrations of the degradation products were measured every hour by a gas chromatograph (model GC-9A, Shimadzu, Kyoto, Japan) equipped with a gas sampler (model MGS-5, Shimadzu). The analytical conditions for the gas chromatograph were a column temperature of 100°C and an injection inlet temperature of 140°C. Nitrogen was used as the carrier gas at a flow rate of 50 ml min^{-1}. The detector was a hydrogen flame ionization detector (FID). The column was a glass column 5 m in length and 3 mm in internal diameter filled with 20% DOP Chromosorb WAW (Technolab S.C. Corp., Osaka, Japan) and 80/100 mesh. Sample volume was 1 ml. The gas chromatograph was calibrated by preparing standard calibration gas from a stock solution of compound A supplied by Maruishi Pharmaceutical Co., Ltd (Osaka, Japan). The coefficients of variation for measurement of compound A concentrations were 2.5%, 2.6% and 2.2% at 5.1, 19.8 and 49.3 ppm of compound A, respectively.

All results are expressed as median (range). Maximum and hourly degradation product concentrations, temperature of soda lime and end-tidal sevoflurane concentrations were measured in each patient, and the PhysioFlex and Modulus groups were compared using the Mann–Whitney *U* test. The non-parametric Spearman's rank correlation analysis was performed to evaluate the relationship between compound A concentration and end-tidal sevoflurane concentration in the PhysioFlex and Modulus groups. $P<0.05$ was considered statistically significant.

Results

There were no differences in age, height or body weight between the two groups (Table 1). The only degradation product of sevoflurane detected was $CF_2=C(CF_3)\text{-}O\text{-}CH_2F$ (compound A). The maximum concentration of compound A in the circuit was 8.5 (5.4–15.9) ppm in the PhysioFlex group and 21.2 (16.5–27.4) ppm in the Modulus group ($P<0.05$). The mean value was 7.3 (4.3–9.9) ppm in the PhysioFlex group and 18.3 (14.5–21.7) ppm in the Modulus group ($P<0.05$). The maximum soda lime temperature was significantly lower in the PhysioFlex group (35.3 (32.3–36.3)°C) than in the Modulus group (44.6 (43.0–47.1)°C) ($P<0.05$).

Compound A concentrations at 1-h intervals were consistently lower in the PhysioFlex group than in the Modulus group (Fig. 1). End-tidal sevoflurane concentrations during determination of degradation products were not different between groups. There was a positive correlation between the concentration of compound A and the end-tidal sevoflurane concentration in the two groups (Fig. 2). There was no correlation between compound A concentrations and the temperature of soda lime in the two groups (data not shown).

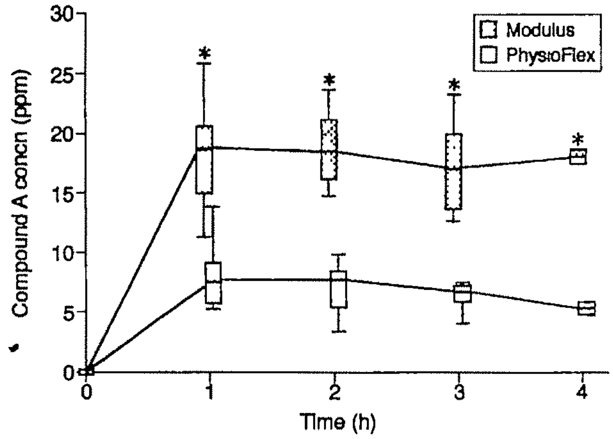


Fig 1 Comparison of compound A concentrations in the PhysioFlex and Modulus groups. Box and whisker plots represent the 10th, 25th, 50th (median), 75th and 90th percentiles of compound A concentrations at each sampling point ($n=8$ in each group). *$P<0.05$ *vs* the PhysioFlex group.

Table 1 Patient characteristics in the PhysioFlex and Modulus groups (median (range))

	Age (yr)	Height (cm)	Weight (kg)
PhysioFlex group	56.5 (21–63)	156.5 (148.2–175.0)	59.9 (49.0–77.5)
Modulus group	54.5 (23–69)	165.0 (146.0–170.1)	62.8 (51.2–78.0)

Discussion

The PhysioFlex anaesthesia machine facilitates quantitative closed system anaesthesia.[7–11] In this anaesthesia machine, the concentration of respiratory gases and the volume in the circle system are controlled automatically by a feedback mechanism. In this study, we measured concentrations of compound A, a degradation product of sevoflurane, using the PhysioFlex under closed system conditions, and compared this with a standard anaesthesia machine at a flow rate of 1 litre min^{-1}.

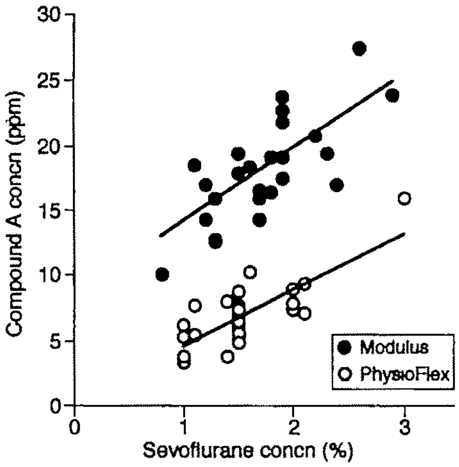


Fig 2 Relationship between compound A and end-tidal sevoflurane concentrations in the PhysioFlex group (Spearman's rho=0.678, $P<0.01$) and the Modulus group (Spearman's rho=0.699, $P<0.01$)

In a closed circuit, there is greater contact between carbon dioxide and soda lime than in a low-flow system, and an increase in the temperature of soda lime can be expected. Moreover, as washout of gas within the system is reduced in a closed circuit, it is speculated that compound A concentrations would be higher than in a low-flow system. Studies have confirmed that lower fresh gas flows produce higher compound A concentrations.[15 19] However, our results showed that compound A concentrations and the temperature of soda lime were lower in the closed system (PhysioFlex group) than in the low-flow system (Modulus group). The circuit gas of the PhysioFlex is moved around unidirectionally by a blower at a rate of 70 litre min^{-1},[7 9 11] which effectively reduces the temperature of soda lime, resulting in a reduction in compound A concentration. Furthermore, the small canister may also contribute to the reduction in soda lime temperature. However, this may not directly contribute to the reduction in compound A, as concentrations of compound A are reported to be essentially unaffected by the amount of soda lime used.[20]

The aim of our study was to evaluate the difference in compound A concentrations between a PhysioFlex and standard anaesthesia machine. Therefore, compound A concentrations should have been compared under closed system conditions. However, we chose a low-flow system on the standard anaesthesia machine for this comparison because effective closed circuit anaesthesia using a standard anaesthesia machine is problematic. The compound A concentration in closed circuit anaesthesia using a standard anaesthesia machine may be predicted from, and will be higher than, the value obtained in low-flow anaesthesia.[12 19] If we compared the two anaesthesia machines under closed system conditions, even larger differences in compound A concentration than the present results would be expected.

A higher concentration of sevoflurane results in a higher concentration of compound A in the circuit.[2 14 16 19 20] Our results also showed a positive correlation between the end-tidal sevoflurane concentration and the concentration of compound A. A higher temperature of soda lime is also expected to result in a higher concentration of compound A,[16–18] but there was no correlation between the temperature of soda lime and compound A concentration. This is probably because the range in temperature was too small to significantly affect compound A concentrations.

Compound A is a dose-dependent nephrotoxin in rats, with a nephrotoxic dose of 150–300 ppm h (inspired concentration×inspired duration).[2–6] However, the nephrotoxic threshold of compound A in humans is controversial. Several studies have reported that low-flow sevoflurane anaesthesia is not associated with abnormalities in renal function.[21–25] Furthermore, there is a species difference in the dose–response to compound A, and the nephrotoxic threshold in humans is greater than that in rats.[26] The apparent species difference in the effects of compound A may be explained by the activity of β-lyase.[27–31] However, Eger and colleagues reported that sevoflurane was associated with glucosuria and proteinuria when used for 4–8 h at low-flow rates, with a threshold for nephrotoxicity of 80–168 ppm h.[32 33] In this study, the mean value of compound A using the PhysioFlex was less than 10 ppm and the duration of anaesthesia was less than 5 h. Therefore, compound A exposure was less than 50 ppm h which is lower than the nephrotoxic threshold. Even if the results of Eger and colleagues are accepted, the 5-h duration of closed circuit anaesthesia using the PhysioFlex is safe based on our results.

The US Federal Drug Administration (FDA) has stated that, because of the limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates below 1 litre min^{-1} in a circle absorber system are not recommended. However, the FDA recommendation cannot be applied to the PhysioFlex system. When fresh soda lime is used, the maximum compound A concentration at a fresh gas flow rate of 3 litre min^{-1} is 8.1 ppm (mean).[15] In our study, when the PhysioFlex was used under closed system conditions, the maximum compound A concentration was 8.5 ppm. Therefore, concentrations of compound A in closed circuit anaesthesia using the PhysioFlex were almost the same as those obtained at a flow rate of 3 litre min^{-1} using a standard anaesthesia machine. The FDA has stated that there is no restriction at fresh gas flow rates >2 litre min^{-1}. Thus sevoflurane anaesthesia using a closed system with a PhysioFlex machine is likely to be safe.

We conclude that concentrations of compound A in closed circuit anaesthesia using the PhysioFlex were lower than those in low-flow anaesthesia using a standard anaesthesia machine. The concentration of compound A in the closed circuit anaesthesia using the PhysioFlex can be maintained at the same level as that obtained at a flow rate of 3 litre min^{-1} using a standard anaesthesia machine.

References

1 Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: A new inhalational anesthetic agent. *Anesth Analg* 1975; **54**: 758–65

2 Morio M, Fujii K, Satoh N, *et al* Reaction of sevoflurane and its degradation products with soda lime: Toxicity of the byproducts *Anesthesiology* 1992; **77**: 1155–64

3 Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats: Effect of a 3-hour administration. *Anesthesiology* 1994, **80**: 556–65

4 Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL. Toxicity of compound A in rats· Effect of increasing duration of administration. *Anesthesiology* 1994; **80**: 566–73

5 Kandel L, Laster MJ, Eger EI II, Kerschmann RL, Martin J. Nephrotoxicity in rats undergoing a one-hour exposure to compound A. *Anesth Analg* 1995; **81**: 559–63

6 Keller KA, Callan C, Prokocimer P, *et al.* Inhalation toxicity study of a haloalkene degradant of sevoflurane, compound A (PIFE), in Sprague–Dawley rats. *Anesthesiology* 1995; **83**: 1220–32

7 Verkaaik AP, Erdmann W. Respiratory diagnostic possibilities during closed circuit anesthesia. *Acta Anaesth Belg* 1990; **41** 177–88

8 Biro P. Anaesthetic gas consumption and costs in a closed system with the PhysioFlex anaesthesia equipment. *Anaesthesist* 1993; **42**: 638–43

9 Verkaaik APK, Van Dijk G. High flow closed circuit anaesthesia. *Anaesth Intensive Care* 1994; **22**: 426–34

10 Hargasser S, Breinbauer B, Kling M, *et al.* Anaesthesia with the closed PhysioFlex system in comparison with conventional anaesthesia procedures. *Anaesthesiol Reanim* 1994; **19**: 149–54

11 Wissing H, Kuhn I, Kessler P. The temperature–humidity profile of PhysioFlex. Study on a model. *Anaesthesist* 1997; **46**: 201–6

12 Bito H, Ikeda K. Closed-circuit anesthesia with sevoflurane in humans: Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit *Anesthesiology* 1994; **80**: 71–6

13 Frink EJ, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR jr. Quantification of the degradation products of sevoflurane in two CO_2 absorbants during low-flow anesthesia in surgical patients. *Anesthesiology* 1992; **77**. 1064–9

14 Bito H, Ikeda K. Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents· Quantification of degradation products in the circuit. *Anesthesiology* 1994; **81**. 340–5

15 Bito H, Ikeda K Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. *Br J Anaesth* 1995; **74**: 667–9

16 Munday IT, Ward PM, Foden ND, Jones RM, Van Pelt FNAM, Kenna JG. Sevoflurane degradation by soda lime in a circle breathing system. *Anaesthesia* 1996; **51**: 622–6

17 Cunningham DD, Huang S, Webster J, Mayoral J, Grabenkort RW. Sevoflurane degradation to compound A in anaesthesia breathing systems. *Br J Anaesth* 1996; **77**. 537–43

18 Ruzicka JA, Hidalgo JC, Tinker JH, Baker MT. Inhibition of volatile sevoflurane degradation product formation in an anesthesia circuit by a reduction in soda lime temperature *Anesthesiology* 1994; **81**: 238–44

19 Fang ZX, Eger EI II. Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit *Anesth Analg* 1995; **81**. 564–8

20 Fang ZX, Kandel L, Laster MJ, Ionescu P, Eger EI II. Factors affecting production of compound A from the interaction of sevoflurane with Baralyme and soda lime. *Anesth Analg* 1996, **82**: 775–81

21 Bito H, Ikeda K. Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia *Anesth Analg* 1996; **82**. 173–6

22 Bito H, Ikeuchi Y, Ikeda K Effects of low-flow sevoflurane anesthsia on renal function: Comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. *Anesthesiology* 1997; **86**: 1231–7

23 Kharasch ED, Frink EJ jr, Zager R, Bowdle TA, Artru A, Nogami WM. Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. *Anesthesiology* 1997; **86**· 1238–53

24 Ebert TJ, Frink EJ, Kharasch ED. Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1 25 minimum alveolar concentration sevoflurane anesthesia in volunteers. *Anesthesiology* 1998; **88**: 601–10

25 Ebert TJ, Messana LD, Uhrich TD, Staacke TS. Absence of renal and hepatic toxicity after four hours of 1.25 minimum alveolar anesthetic concentration sevoflurane anesthesia in volunteers. *Anesth Analg* 1998; **86**: 662–7

26 Mazze RI, Friedman M, Delgado-Herrera L, Galvez ST, Mayer DB Toxicity of compound A plus sevoflurane compared with isoflurane in non-human primates. *Anesthesiology* 1998; **89**. A490

27 Iyer RA, Anders MW. Cysteine conjugate β-lyase-dependent biotransformation of the cysteine s-conjugates of the sevoflurane degradation product compound A in human, nonhuman primate, and rat kidney cytosol and mitochondria. *Anesthesiology* 1996; **85**· 1454–61

28 Iyer RA, Frink EJ, Ebert TJ, Anders MW. Cysteine conjugate β-lyase-dependent metabolism of compound A (2-[fluoromethoxy]-1,1,3,3,3-pentafluoro-1-propene) in human subjects anesthetized with sevoflurane and in rats given compound A *Anesthesiology* 1998; **88**: 611–18

29 Uttamsingh V, Iyer RA, Baggs RB, Anders MW. Fate and toxicity of 2-[fluoromethoxy]-1,1,3,3,3-pentafluoro-1-propene (compound A)-derived mercapturates in male, Fischer 344 rats *Anesthesiology* 1998; **89**: 1174–83

30 Kharasch ED, Thorning D, Garton K, Hankins DC, Kilty CG. Role of renal cysteine conjugate β-lyase in the mechanism of compound A nephrotoxicity in rats *Anesthesiology* 1997; **86**: 160–71

31 Kharasch ED, Hoffman GM, Thorning D, Hankins DC, Kilty CG. Role of renal cysteine conjugate β-lyase pathway in inhaled compound A nephrotoxicity in rats. *Anesthesiology* 1998; **88**· 1624–33

32 Eger EI II, Koblin DD, Bowland T, *et al.* Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. *Anesth Analg* 1997, **84**: 160–8

33 Eger EI II, Gong D, Koblin DD, *et al* Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. *Anesth Analg* 1997; **85**. 1154–63

British Journal of Anaesthesia **84** (3) 354–7 (2000)

Effects of the sitting position on the distribution of blood volume in patients undergoing neurosurgical procedures

W. Buhre[1], A. Weyland[1], K. Buhre[1], S. Kazmaier[1], K. Mursch[2], M. Schmidt[1], M. Sydow[1] and H. Sonntag[1]

[1]Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin and [2]Klinik und Poliklinik für Neurochirurgie, Georg-August-Universität Göttingen, Robert-Koch-Str. 40, D-37075 Göttingen, Germany

The use of the sitting position in neurosurgery is often associated with decreased arterial pressure (MAP) and stroke volume index (SVI). A shift in blood from the intra- to the extrathoracic compartment may be responsible for this cardiovascular response. However, little is known of the amount of shift in blood volume after transfer from the supine to the sitting position. Therefore, we measured simultaneously changes in intrathoracic blood volume (ITBV) caused by a change in body position in anaesthetized patients. Measurements of cardiac index (CI), ITBV, pulmonary (PBV) and total circulating (TBV_{circ}) blood volumes were performed in the supine and sitting position. CI, ITBV, PBV and TBV_{circ} were measured using a thermo–dye dilution technique. Fluid input was restricted to 14 ml kg^{-1} before induction of anaesthesia. Change in body position caused a significant decrease in ITBV and was accompanied by a significant decrease in CI, SVI and MAP. Changes in ITBV correlated (r=0.78) with changes in SVI. Thus a change in blood volume distribution between the intra- and extrathoracic compartment occurred after a change from the supine to the sitting position. Indicator dilution enables quantification of this shift and may be helpful in guiding fluid therapy in selected patients.

Br J Anaesth 2000; **84**: 354–7

Keywords: position, sitting; position, effects; blood, volume; surgery, neurological; measurement techniques, indicator dilution

Accepted for publication: September 23, 1999

Although there is much debate about the advantages of the sitting position in neurosurgery, this position is used routinely in many institutions for patients undergoing surgery in the posterior fossa.[1 2] In addition to the increased risk of air embolism, the sitting position is often associated with haemodynamic instability, in particular a decrease in mean arterial blood pressure, stroke volume index and cardiac index.[3–7] It can be assumed that the cardiovascular effects of the sitting position are caused mainly by a reduction in cardiac preload.[7] However, no data are available on the quantity of blood volume redistribution from the intra- to the extrathoracic compartment in anaesthetized patients undergoing neurosurgical procedures in the sitting position. Thus in this prospective, controlled clinical study, we have investigated the effects of change from the supine to the sitting body position on the distribution of blood volume using an indicator dilution technique.

Patients and methods

We studied 10 patients (seven females, three males, ASA II) undergoing elective neurosurgical procedures performed in the sitting position. The study was approved by the Institutional Review Board Committee and patients gave written informed consent. None of the patients had a history of cardiopulmonary, renal or liver disease and none was receiving cardiac medications before operation.

Premedication comprised flunitrazepam 1–2 mg orally on the evening before surgery and 1 h before induction of anaesthesia. After arrival, ECG leads II and V5 were attached to the patient (Sirecust 961, Siemens, Germany). Before induction of anaesthesia, infusions of crystalloid 7 ml kg^{-1} (Eufusol, Braun Melsungen, Germany) and colloid 7 ml kg^{-1} (Gelafundin, Braun Melsungen, Germany) were administered via a peripheral venous line over a period of 30 min. No more fluids were given during the study, except for 200 ml of ice-cooled solution for thermodilution and dye dilution measurements. Under local anaesthesia a subclavian venous line (12 F, Arrow Int., Reading, PA, USA) was inserted and its tip advanced to lie in the right atrium. The correct position of the right atrial catheter was verified by transoesophageal echocardiography when anaesthesia was instituted. For measurements of cardiac output (CO), intrathoracic blood volume (ITBV), pulmonary blood volume (PBV) and total circulating blood volume (TBV_{circ}), a combined 4-French gauge fibreoptic-thermistor catheter

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

(Pulsiocath PV 2024, Pulsion Medical Systems, Germany) was inserted 40 cm up into the descending aorta via a 5-French gauge introducer (Arrow Int., Reading, USA) in the left femoral artery. The fibreoptic catheter was connected to a commercially available opto-electronic device (COLD-System, Pulsion Medical Systems, Germany) which allows simultaneous detection of thermodilution and dye dilution curves.[8 9]

General anaesthesia was induced with fentanyl 6 $\mu g\ kg^{-1}$ and midazolam 0.1 $mg\ kg^{-1}$. Pancuronium 0.1 $mg\ kg^{-1}$ was administered to facilitate tracheal intubation. Anaesthesia was maintained with fentanyl 10 $\mu g\ kg^{-1}\ h^{-1}$ and midazolam 150 $\mu g\ kg^{-1}\ h^{-1}$. Vasoactive drugs or inhalation anaesthetics were not given. After tracheal intubation, patients' lungs were ventilated mechanically in a volume-controlled mode with a positive end-expiratory pressure (PEEP) of 5 cm H_2O. Respiratory minute volume was adjusted to maintain normocapnia (Pa_{CO_2} 4.8–6.0 kPa). Inspired oxygen fraction (FI_{O_2}) was 0.5. No further ventilatory adjustments were made during the study.

Standard haemodynamic variables, including heart rate (HR), mean arterial (MAP) and right atrial (RAP) pressures were obtained and indicator dilution measurements were performed under stable haemodynamic conditions after induction of anaesthesia (supine position) and after raising the patient to a 45° sitting position (sitting position). Pressure transducers were positioned at the midaxillary level when patients were supine and at the level of the fifth intercostal space anteriorly when they were sitting. Arterial and venous blood samples were obtained at each measurement to determine haemoglobin content, oxygen saturation (OSM-3 Hemoximeter, Radiometer, Denmark) and blood-gas analysis (ABL 500 Blood Gas Analyser, Radiometer, Denmark).

Thermodilution and dye dilution curves were obtained by triple bolus injection of 20 ml of ice-cooled saline solution and two additional bolus injections of 20 ml of ice-cooled indocyanine green dye (ICG) 1.25 $mg\ ml^{-1}$ into the right atrium. Injections were spread randomly over the respiratory cycle. The resulting thermodilution and dye dilution curves obtained in the aorta were digitized and stored on a microcomputer (COLD-System, Pulsion Medical Systems, Germany). CO was assessed using the thermodilution technique. Intrathoracic blood volume (ITBV) was calculated from CO and the mean transit time of the indicator (mtt_{dye}) through the thoracic compartment of the circulation.[9]

$$ITBV = CO \times mtt_{dye}\ (ml) \qquad (1)$$

PBV was calculated from the product of the exponential downslope time ($t_{dt\ dye}$) of the dye curve obtained in the aorta and CO.[9] The downslope time is defined as the reciprocal value of the time constant characterizing the downslope of the indicator dilution curve.[9]

$$PBV = CO \times t_{dt\ dye} \qquad (2)$$

Table 1 Data on blood gases and airway pressure during the study (mean (SD)) Hb=Haemoglobin, HCT=haematocrit, Sa_{O_2}=arterial oxygen saturation, Pa_{O_2}=arterial oxygen partial pressure, Pa_{CO_2}=arterial carbon dioxide partial pressure, Paw-peak=peak airway pressure, Paw-mean=mean airway pressure

	Supine position	**Sitting position**
Hb (g dl^{-1})	11.7 (1.5)	11.8 (1 7)
HCT (%)	35 8 (4 5)	35.8 (4.9)
Sa_{O_2} (%)	99 1 (0.5)	98 8 (0.9)
Pa_{O_2} (kPa)	34 9 (10.3)	28 3 (7.6)
Pa_{CO_2} (kPa)	5.7 (0 5)	5 4 (0 3)
Paw-peak (mbar)	24.8 (5.1)	24.4 (4 9)
Paw-mean (mbar)	10 (1.0)	9 9 (0 9)

Table 2 Haemodynamic variables (mean (SD)). HR=Heart rate, MAP=mean arterial pressure, RAP=right atrial pressure, CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance index, ITBV=intrathoracic blood volume, PBV=pulmonary blood volume, TBV_{circ}=total circulating blood volume. *Significant influence of the sitting position ($P \leq 0.05$)

	Supine position	**Sitting position**
HR (beat min^{-1})	68 (5)	63 (4)*
MAP (mm Hg)	92 (14)	83 (18)*
RAP (mm Hg)	6 (2.6)	3 (3 2)*
CI (litre $min^{-1}\ m^{-2}$)	2 4 (0.4)	1.8 (0.3)*
SVI (ml m^{-2})	36 (6)	29 (5)*
SVRI (dyn s $cm^{-5}\ m^2$)	2853 (359)	3509 (480)*
ITBV (ml m^{-2})	626 (97)	534 (89)*
PBV (ml m^{-2})	151 (17)	141 (15)
TBV (ml kg^{-1})	58 (10)	60 (13)

Total circulating blood volume (TBV_{circ}) was calculated simultaneously from the aortic dye dilution curves.[10] Complete mixing of the indicator in blood was assumed to occur after 80 to 150 s. The concentration of ICG at injection time ($C_{0(ICG)}$) was determined by monoexponential extrapolation of the dye dilution curve after complete mixing of indicator.[10] According to the principle of mass conservation, TBV_{circ} was calculated by the following equation[11]:

$$TBV_{circ} = m_{ICG}/C_{0(ICG)}\ (ml) \qquad (3)$$

m_{ICG}=amount of injected ICG

All volume- and flow-related variables were normalized to body surface area or body weight.

Statistical analysis

Results are expressed as mean (SD). Paired Student's t tests were used to compare data obtained before and after transfer from the supine to the sitting position. $P \leq 0.05$ was considered statistically significant. All statistical procedures were performed on a microcomputer using the SPSS/PC+ statistical software package.

Results

Mean age of patients was 47 (range 27–68) yr. Mean body weight and height were 69 (SD 10) kg and 168 (5) cm, respectively. Cardiopulmonary data and data on blood gases and haemoglobin content are presented in Tables 1 and 2 and Figures 1 and 2, respectively.

Haemoglobin content and blood gases remained constant

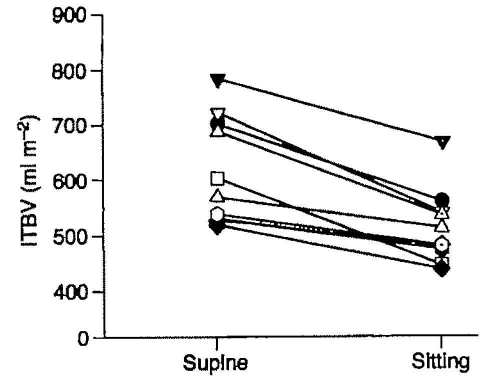


Fig 1 Relative changes in intrathoracic blood volume (ITBV) for individual patients. Each patient is depicted by a different symbol. In all patients a decrease in ITBV was observed. Mean difference of ITBV between supine and sitting positions was 14%.

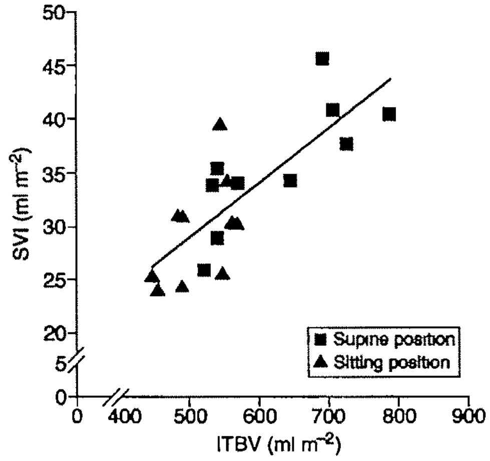


Fig 2 Correlation between relative changes in stroke volume index (SVI) and intrathoracic blood volume (ITBV) associated with transfer from the supine to the sitting body position in anaesthetized patients (r=0.78).

during the study (Table 1). MAP and RAP decreased significantly when the patient position changed from the supine to the sitting. Figure 1 summarizes our findings with regard to ITBV. Indicator dilution measurements demonstrated that the transfer to the sitting position resulted in a significant decrease in ITBV by 14% (Fig. 1) in CI and SVI by 24% and 17%, respectively (Table 2). In contrast, PBV remained almost unchanged. Systemic vascular resistance index (SVRI) increased by 14% (Table 2). Correlation analysis revealed a linear relationship between relative changes in SVI and ITBV (r=0.78) (Fig. 2). In contrast, there was no correlation between changes in RAP and changes in SVI (r=0.45). Circulating blood volume (TBV_{circ}) did not change significantly throughout the study. Mean and peak airway pressures did not differ between the supine and sitting positions (Table 1). No catheter-related complications or allergic reactions were observed during the study.

Discussion

In our study, we found that a shift in blood volume of 14% from the intra- to the extrathoracic space occurred after change from the supine to the sitting position, resulting in a significant decrease in CI by 24 %. Also, volume loading with a total of 14 ml kg^{-1} of crystalloid and colloid fluids could not entirely prevent the haemodynamic instability of this procedure.

The sitting position in neurosurgery is associated with specific risk factors.[1] Haemodynamic instability is often observed, in particular in patients with limited cardiac reserve.[7] Several studies have investigated the haemodynamic effects associated with transfer from the supine to the sitting position in healthy subjects or patients undergoing neurosurgical procedures.[5–7] In most studies, arterial hypotension, defined as a decrease in mean arterial pressure of >10% or a decrease in systolic arterial pressure of >20% was observed with an incidence of 5–32%.[3–5]

The choice of anaesthetic technique may have a significant influence on haemodynamic stability in anaesthetized patients in the sitting position.[7] Dalrymple, MacGowan and MacLeod observed a 37% decrease in CI when anaesthesia was maintained with nitrous oxide and fentanyl after raising into the sitting position.[6] The decrease in CI in our patients was less pronounced than in the study of Dalrymple, MacGowan and MacLeod. This is most likely because different fluid regimens were used.[6] More recently, Marshall, Bedford and Miller studied the cardiovascular response to the sitting position.[7] Patients received either enflurane–nitrous oxide, halothane–nitrous oxide, fentanyl–droperidol–nitrous oxide or morphine–nitrous oxide for maintenance of anaesthesia. A significant decrease in CI was observed in all groups after change from the supine to the sitting position. The combination of morphine–nitrous oxide caused the least change.[7] However, haemodynamic stability in this study may have been related to high plasma concentrations of catecholamines because of inadequate depth of anaesthesia. In our study, maintenance of anaesthesia was performed with fentanyl combined with continuous infusion of midazolam.

Our investigation differed from previous studies in two ways. First, we measured simultaneously direct volumetric variables of intra- and extrathoracic blood volume compartments to determine the net effects of the sitting position on blood volume distribution in humans. Second, fluid input was standardized and restricted to 7 ml kg^{-1} of a crystalloid and 7 ml kg^{-1} of a colloid solution before the first set of measurements.

Indicator dilution has gained acceptance for bedside measurement of intrathoracic, pulmonary and total circulating blood volume.[9 10 12 13] As ITBV primarily represents the blood volume of the heart and pulmonary circulation, it seems a better indicator of cardiac preload than filling pressures.[8 12 14 15] In our patients, a decrease in ITBV after repositioning was consistently accompanied by a decrease in SVI whereas no linear correlation between RAP and SVI was observed. Thus measurement of ITBV before and after change in body position enables titration of volume therapy to optimize blood volume and SVI. This may be of clinical value in other situations in which blood volume shifts occur, such as inversed ratio ventilation and sepsis-induced vasodilatation.

Perkins-Pearson, Marshall and Bedford studied the effects of patient position and anaesthesia on right and left heart filling pressures using pulmonary artery catheters.[16] They found a decrease in PCWP in the sitting position whereas RAP remained unchanged. and they attributed this reduction to a decrease in pulmonary blood volume.[16] By directly measuring PBV, we could not verify the observation of Perkins-Pearson, Marshall and Bedford as PBV remained almost unchanged in our patients, whereas RAP decreased significantly. However, it is possible that the tip of the pulmonary artery catheters in their study may have become lodged in a part of the lung where PCWP reflects airway pressure rather than left atrial pressure.

In our study, fluid input was restricted to a total of 14 ml kg^{-1} of crystalloid and colloid solutions. As indicated by the decrease in ITBV, this amount of fluid was not able to compensate for the shift of blood from the intra- to the extrathoracic compartment. However, without any attempt to volume load the patients, the changes may have been more pronounced.

Because of the short half-life of the crystalloid solution, significant amounts of fluid may have been lost in the extravascular space, possibly influencing measurements of ITBV and PBV. However, measurements of TBV_{circ} did not differ significantly between values obtained before and after transfer from supine to sitting, suggesting that no significant loss of fluid from the intravascular compartment occurred during the study. The decrease in ITBV in our patients thus primarily quantified the amount of blood shifted from the intra- to the extrathoracic compartment.

In summary, we have demonstrated that intrathoracic blood volume decreased by 14% after transfer from the supine to the sitting position, whereas total circulating blood volume remained constant. This indicates a volume shift from the intra- to the extrathoracic compartment. Concomitant changes in arterial pressure and stroke volume index are thus caused primarily by a reduction in cardiac preload, which can be monitored by serial indicator dilution measurements of intrathoracic blood volume.

References

1 Albin MS, Babinski M, Maroon JC, Janetta PJ. Anaesthetic management of posterior fossa surgery in the sitting position. *Acta Anaesthesiol Scand* 1976; **20**, 117–28

2 Elton RJ, Howell SC. The sitting position in neurosurgical anaesthesia: a survey of British practice in 1991. *Br J Anaesth* 1994; **73**: 247–8

3 Black S, Ockert DB, Oliver WC, Cucciara RK. Outcome following posterior fossa craniectomy in patients in the sitting or horizontal position *Anesthesiology* 1980; **69**. 49–56

4 Matjasko J, Petrozza P, Cohen M, Steinberg P. Anaesthesia and surgery in the seated position. *Neurosurgery* 1985; **17**: 695–702

5 Young ML, Smith DS, Murtagh F, *et al* Comparison of surgical and anesthetic complcations in neurosurgical patients experiencing venous air embolism in the sitting position. *Neurosurgery* 1986, **18**. 157–61

6 Dalrymple DG, MacGowan SW, MacLeod GF Cardiorespiratory effects of the sitting position in neurosurgery. *Br J Anaesth* 1979, **51**: 1079–82

7 Marshall WK, Bedford RF, Miller ED. Cardiovascular responses in the seated position—impact of four anesthetic techniques. *Anesth Analg* 1983; **62**: 648–53

8 Hoeft A, Schorn B, Weyland A, *et al.* Bedside assessment of intravascular volume status in patients undergoing coronary bypass surgery. *Anesthesiology* 1994; **81**: 76–86

9 Hachenberg T, Tenling A, Rothen HU, *et al.* Thoracic intravascular and extravascular fluid volumes in cardiac surgical patients. *Anesthesiology* 1993, **79**: 976–84

10 Kisch H, Leucht S, Lichtwarck AM, Pfeiffer UJ. Accuracy and reproducibility of the measurement of actively circulating blood volume with an integrated fiberoptic monitoring system. *Crit Care Med* 1995; **23**: 885–93

11 Zierler K. Theoretical basis of indicator dilution methods for measuring flow and volume. *Circ Res* 1962, **10**: 393–407

12 Lichtwarck-Aschoff M, Beale R, Pfeiffer UJ. Central venous pressure, pulmonary artery occlusion pressure, intrathoracic blood volume, and right ventricular end-diastolic volume as indicators of cardiac preload. *J Crit Care* 1996; **11**: 180–8

13 Lichtwarck-Aschoff M, Zeravik J, Pfeiffer UJ. Intrathoracic blood volume accurately reflects circulatory volume status in critically ill patients with mechanical ventilation. *Intensive Care Med* 1992; **18**: 142–7

14 Echt M, Duweling J, Gauer OH, Lange L Effective compliance of the total vascular bed and the intrathoracic compartment derived from changes in central venous pressure induced by volume changes in man. *Circ Res* 1973; **34** 61–8

15 Arndt JO. The low pressure system: the integrated function of veins. *Eur J Anaesthesiol* 1986; **3**: 343–70

16 Perkins-Pearson NAK, Marshall WK, Bedford RF. Atrial pressure in the seated position. *Anesthesiology* 1982; **57**: 493–7

British Journal of Anaesthesia **84** (3) 358–62 (2000)

Effects of fenoterol and ipratropium on respiratory resistance of asthmatics after tracheal intubation†

R. S. C. Wu[1]*, K. C. Wu, T. K. M. Wong, Y. H. Tsai, R. K. S. Cheng, M. J. Bishop[2] and P. P. C. Tan[3]

China Medical College Hospital, Taichung, Taiwan, Republic of China

Present addresses: [1]China Medical College, Taichung, Taiwan. [2]Puget Sound VA Health Care System (Pulmonary and Critical Care, Adjunct), University of Washington School of Medicine, Seattle, Washington, USA. [3]Chang Gung University, Taipei, Taiwan, Republic of China

**Corresponding author: Department of Anesthesiology, No. 2 Yuh-Der Road, China Medical Hospital, Taichung, Taiwan, ROC*

We have studied the effects of a beta-agonist, fenoterol, and a cholinergic antagonist, ipratropium, on post-intubation total respiratory system resistance (*Rrs*) in asthmatics who developed increased *Rrs* after tracheal intubation. Sixteen stable asthmatics in whom *Rrs* increased after intubation were allocated randomly to receive either 10 puffs of fenoterol (group F) or 10 puffs of ipratropium (group IB) via a metered dose inhaler 5 min after intubation. Anaesthesia was induced and maintained with propofol i.v. *Rrs* was recorded before treatment and again 5, 15 and 30 min after treatment. *Rrs* decreased significantly from pretreatment values by mean 53 (SD 8)%, 53 (7)% and 58 (6)% at 5, 15 and 30 min, respectively, in group F, but declined by only 12 (6)%, 15 (4)% and 17 (5)% in group IB. At all times after treatment, patients in the fenoterol group had significantly lower *Rrs* values than those in the ipratropium group. We conclude that increased *Rrs* after tracheal intubation in asthmatics can be reduced effectively by treatment with fenoterol. A secondary finding of our study was that even after induction of anaesthesia with propofol, patients with a history of asthma may develop high *Rrs*.

Br J Anaesth 2000; **84**: 358–62

Keywords: pharmacology, ipratropium; sympathetic nervous system, fenoterol; complications, bronchoconstriction; lung, bronchus; intubation tracheal; asthma

Accepted for publication: October 25, 1999

After tracheal intubation, mechanical stimulation of receptors in the nose, larynx[1] or airways[2] may precipitate reflex bronchospasm and mucus secretion, most likely via vagal pathways.[3] Asthmatic patients have hyper-reactive airways and hence are presumably at greater risk of such an event.

Management of airway reactivity during anaesthesia includes prophylaxis with an inhaled beta$_2$ agonist,[4] deep anaesthesia[5] and administration of a beta agonist, although there are few data on the efficacy of therapy.[6] Because intraoperative bronchospasm is probably partly vagally mediated, anticholinergic therapy has also been proposed. Ipratropium, a cholinergic antagonist, is a quaternary ammonium derivative of atropine which, as an aerosol, is highly specific and virtually free of side effects even in high doses.[7] Inhaled ipratropium is effective in reversing cholinergic bronchoconstriction in anaesthetized, paralysed rabbits.[8] In this study, we assessed the efficacy of fenoterol and ipratropium in treating asthmatic patients who develop intraoperative bronchospasm.

Patients and methods

This study was carried out with the approval of the Human Subjects Review Board of Chang Gung Memorial Hospital. All patients were of normal size, undergoing surgery on the extremities, had a minimum 3-yr history of clinically diagnosed asthma and were treated regularly with beta adrenergic agents. Subjects with a history of heart disease, or recent or chronic respiratory disease other than asthma were excluded. Informed consent was obtained from all subjects.

Pulmonary function was assessed before operation by the same anaesthetist. With the patient in the upright position, a hand-held spirometer (Vitalograph, Buckingham, UK) was used to measure forced expiratory volume in 1 s

---

†Presented in part at the 71st Clinical and Scientific Congress of the International Anaesthesia Research Society, San Francisco, CA, USA, March 14–18, 1997.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

(FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR). Calibration of the spirometer was performed with a 1-litre calibration syringe (Vitalograph, Buckingham, UK) before the subject was tested. Measurements were made in triplicate, and the greatest value was accepted.

No premedication was given. Anaesthesia was induced with propofol 2.5 mg kg^{-1} i.v., and vecuronium 0.15 mg kg^{-1} i.v. was given to facilitate tracheal intubation with a 7.5-mm internal diameter tracheal tube. An infusion of propofol 9 mg kg^{-1} h^{-1} was started immediately after intubation to maintain general anaesthesia. When all study measurements were completed, opioids and inhalation anaesthetics were administered to provide general anaesthesia for the surgical procedure. Patients' lungs were ventilated with oxygen using a Drager-Narkomed II ventilator (North American Drager, Pennsylvania, USA) at a tidal volume of 600 ml and ventilatory frequency of 10 bpm. The inspiratory flow of the ventilator was set to produce a peak inspiratory flow rate of 0.5 litre s^{-1}.

Resistance of the respiratory system (*R*rs) was measured with a CP-100 pulmonary function monitor (Bicore, Irvine, CA, USA). The CP-100 pulmonary function monitor is a monitoring device consisting of a flow transducer (VarFlex) and an oesophageal balloon catheter which allows breath-by-breath measurement of tidal volume (V_T), airway flow ($\dot{V}$), transpulmonary pressure (airway minus oesophageal pressure) and airway pressure (*P*aw). The flow transducer was connected to the ventilation circuit between the tracheal tube and Y-piece. The oesophageal balloon catheter was left exposed to ambient pressure to measure *R*rs. Measurement of *R*rs was based on pressure and flow measurements in the airway. Resistance measurements were calculated using the isovolume method (the difference in airway pressure divided by the sum of the flows obtained at the same volume during both inspiration and expiration)[9–12] and included the resistance of the tracheal tube. The CP-100 monitor is equipped with self-diagnostic hardware tests which perform self-calibration of the measuring system.

The isovolume method of resistance measurement is a technique applicable to patients undergoing mechanical ventilation and is based on measuring airway pressure and flow at identical volumes during inspiration and exhalation. Inspiratory pressure (P_I) is a function of respiratory compliance (*C*), flow ($\dot{V}_I$) and resistance (*R*). Expiratory pressure (P_E) is a function of respiratory compliance (*C*), expiratory flow ($\dot{V}_E$) and resistance (*R*). Using *V* to represent lung volume above FRC, the equations are:

$$P_I = C/V + R \times \dot{V}_I$$

and

$$P_E = C/V + R \times \dot{V}_E$$

C/V is identical in each equation when considering identical volumes. Subtracting these two equations gives:

$$P_I - P_E = R \times (\dot{V}_I - \dot{V}_E) \text{ or } R = (P_I - P_E)/(\dot{V}_I - \dot{V}_E)$$

This method measures resistance during both inhalation and exhalation and provides a mean *R*rs for the two phases.

A total of 20 patients consented to the study. Patients remained in the study only if they developed an *R*rs at 5 min that was 2 SD above our previously established mean for non-asthmatics (8.5 (1.5) cm H_2O $litre^{-1}$ s^{-1}).[13] The 16 patients who met this admission criterion were allocated randomly to one of two groups. Through an Aerochamber spacer (Monaghan Medical Corporation, Plattsburgh, NY, USA) attached between the Y-piece of the anaesthesia ventilatory circuit and the proximal end of the inspiratory limb, patients in group F were treated with 10 puffs of inhaled fenoterol (0.2 mg $puff^{-1}$, Boehringer Ingelheim, Berkshire, UK) from a metered dose inhaler (MDI) 5 min after intubation. Patients in group IB were given 10 MDI puffs of ipratropium (0.02 mg $puff^{-1}$, Boehringer Ingelheim, Berkshire, UK). The flow transducer between the tracheal tube and Y-piece was temporarily disconnected from the ventilation circuit during drug delivery to prevent deposition of the medication on the transducer and reduction of drug delivery to the patient. All MDI canisters were labelled with numbers and covered with tape before the start of the study so as to appear identical. The same assistant, who was not an investigator, delivered all medications. The anaesthetist performing the study did not have any knowledge of the type of medications in the canister. All aerosol puffs were given at a rate of 2 puff min^{-1} and the canister was shaken before each puff.

Heart rate, mean arterial pressures and *R*rs were monitored and recorded at 5 min after intubation and at 5, 15 and 30 min after delivery of the last puff of inhaled medication.

Statistical analysis

Patient data and results from preoperative pulmonary function tests were compared between groups for statistical significance using the Student's *t* test for unpaired data. Within-group data on systolic arterial pressure, heart rate and *R*rs were compared using repeated-measures analysis of variance, and specific differences were tested using the Student's *t* test. $P<0.05$ was considered significant. Data are presented as mean (SD).

Results

Patient characteristics are presented in Table 1. There were three patients in group F and two in group IB who were unable to sit up to perform the pulmonary function test because of pain or inability to cooperate. Preoperative pulmonary function tests were largely within normal limits—only two patients had an FEV_1/FVC of less than 0.75. All subjects had a history of treatment with bronchodilators but did not receive treatment for at least 12 h before surgery.

Haemodynamic measurements were notable only for an increase in heart rate after treatment in group F (Table 2).

Table 1 Patient characteristics in the fenoterol (group F) and ipratropium (group IB) groups (mean (SD or range), number or [predicted group means])

	Group F	Group IB
n	8	8
Age (yr)	35.8 (21–67)	38.3 (23–60)
Sex (male)	7	7
Weight (kg)	67.9 (11.8)	60.1 (5.2)
Height (cm)	166.3 (3.1)	162.8 (6.6)
Smoking habits		
Non-smokers	1	1
<1 pack/day	2	3
>1 pack/day	5	4
Asthma duration (yr)		
3–5	1	2
>5	7	6
Preoperative	5	6
pulmonary function		
FVC (litre)	3.8 (0.3) [4.3]	3.7 (0.6) [4.0]
FEV_1 (litre)	3.2 (0.5) [3.5]	3.0 (0.7) [3.3]
FEV1/FVC (%)	84.2 (4.9)	80.8 (9.3)
PEFR (litre min^{-1})	500.8 (148.3) [620]	446.7 (166.0) [610]

All patients developed an *R*rs value at least 2 SD above our previously established mean value (8.5 (1.5) cm H_2O $litre^{-1}$ s^{-1} for healthy patients),[13] confirming the presence of hyper-reactive airways. The lowest Rrs value after intubation was 14.2 cm H_2O $litre^{-1}$ s^{-1}.

*R*rs 5 min after intubation was 30.6 (10.9) and 22.9 (7.6) cm H_2O $litre^{-1}$ s^{-1} in groups F and IB, respectively. After fenoterol treatment, *R*rs decreased to 13.1 (5.2), 13.0 (4.8) and 11.5 (3.5) cm H_2O $litre^{-1}$ s^{-1} at 5, 15 and 30 min after treatment, respectively ($P<0.01$ *vs* *R*rs 5 min after intubation). After treatment with ipratropium, *R*rs declined to 20.7 (9.5), 19.5 (6.9) and 19.3 (8.1) cm H_2O $litre^{-1}$ s^{-1} at 5, 15 and 30 min after treatment, respectively ($P<0.05$ for *R*rs at 15 and 30 min *vs* 5 min after intubation). *R*rs 30 min after treatment represented a 58 (6)% decrease from 5 min after intubation for fenoterol compared with only 17 (5)% for ipratropium (Fig. 1). The percentage decrease in *R*rs for fenoterol was significantly greater than that for ipratropium at all times ($P<0.05$).

Discussion

The important findings of our study were that 10 MDI puffs of fenoterol attenuated tracheal intubation-induced bronchoconstriction in asthmatic patients whereas 10 MDI puffs of ipratropium had a significantly less effect, despite presumed cholinergic mechanisms for bronchoconstriction. A secondary finding was that despite induction of anaesthesia with propofol, 16 of 20 patients with a history of asthma developed high *R*rs values after tracheal intubation.

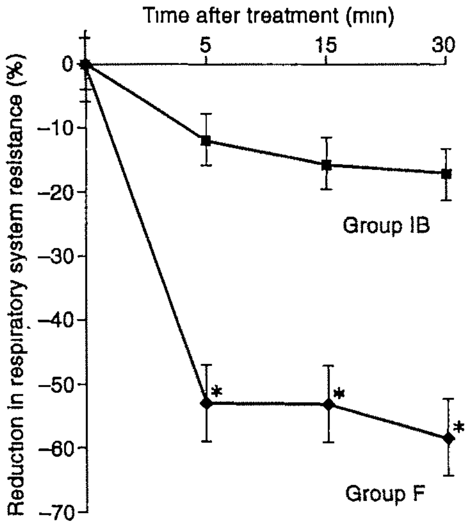


Fig 1 Percentage reduction in total respiratory system resistance (*R*rs) at different times after delivery in the fenoterol (group F) and ipratropium (group IB) groups. Significantly greater reduction in respiratory system resistance was seen after inhaled fenoterol than after inhaled ipratropium (*$P<0.05$).

Anaesthesia was induced with a relatively high dose of propofol which has been shown to minimize resistance in non-asthmatics.[13 14] There was no prevention of airway constriction other than administration of propofol. In asthmatics, propofol causes less wheezing 5 min after intubation compared with barbiturate induction.[15] Our study demonstrated that this protection was not absolute in asthmatic patients and that even propofol induction did not fully prevent high resistance immediately after tracheal intubation.

We excluded patients undergoing non-peripheral surgery to avoid any effect on lung volume from retractor placement or thoracic manipulation. We measured *R*rs instead of *R*L because of its reproducibility in the anaesthetized, paralysed patient and simplicity of measurement, requiring only airway pressure and flow data. The supine position may influence oesophageal pressure readings and decrease accuracy, and technical difficulties caused by oesophageal secretions and catheter movement can make measurements of *R*L less reproducible. Under anaesthesia and neuromuscular paralysis, there is a correlation of 0.9998 between *R*L and *R*rs in rabbits.[8] The difference between *R*rs and *R*L is the resistance of the chest wall, which is constant in anaesthetized, paralysed subjects. Given the inherent difficulties of the oesophageal catheter, *R*rs provides more reliable data. There is substantial evidence that what we

Table 2 Haemodynamic data in the fenoterol (group F) and ipratropium (group IB) groups (mean (SD)). *$P<0.05$ *vs* 5 min after intubation

	Group	5 min after intubation	5 min after treatment	15 min after treatment	30 min after treatment
Heart rate (beat min^{-1})	F	82.9 (11.1)	112.9 (12.2)*	115.4 (11.2)*	112.3 (10.4)*
	IB	85.8 (11.6)	79 (14.7)	76.5 (14.4)	79.5 (18.6)
Arterial pressure (mm Hg)	F	89.1 (11.8)	80.5 (15.5)	82.9 (17.5)	85.9 (18.3)
	IB	99.6 (7.3)	90.4 (11.9)	89.9 (12.3)	96.1 (19.2)

term bronchoconstriction actually represents increases in both airway and tissue components of resistance.[16] Clinically, this is a minor consideration as both components of resistance seem to respond similarly to treatment. As bronchospasm after intubation is an acute response and often requires immediate treatment, we examined the effects of both drugs for the first 30 min after medication to study the efficacy of both drugs in relieving this type of response.

The isovolume method of resistance, as performed in our study, includes resistance of the tracheal tube. At the flow used, the approximate value for a 7.5-mm tracheal tube is 4 cm H_2O litre^{-1} s^{-1}.[9] When this constant is subtracted from the resistance values in groups F and IB, values of 26 cm H_2O litre^{-1} s^{-1} for group F and 19 cm H_2O litre^{-1} s^{-1} for group IB are obtained. This compares with our historical value of 4 cm H_2O litre^{-1} s^{-1} in normal patients (8.5 minus 4 cm H_2O litre^{-1} s^{-1})[13] and suggests that the actual magnitude of the increases in resistance were five- to six-fold in these patients.

The increase in heart rate was probably related to systemic absorption of fenoterol. Our changes in heart rate corresponded with studies in non-anaesthetized patients and may reflect in part less than complete beta$_2$ selectivity.[17] Alternatively, this may represent peripheral vasodilatation, a beta$_2$ agonist effect.

Our finding that fenoterol was significantly more efficacious than ipratropium does not rule out a cholinergic mechanism for the post-intubation increase in resistance. The finding that fenoterol is effective in treating the airway resistance response to tracheal intubation supports other studies showing that beta adrenergic agents can reverse bronchoconstriction caused by a cholinergic stimulus.[18] Cholinergic agonists induce increased tone by binding to smooth muscle cell surface receptors that operate via stimulatory G-protein and ultimately result in Ca^{2+} release from endoplasmic reticulum, leading to muscle contraction. In addition, they can inhibit adenylate cyclase. Beta agonists are thought to relax smooth muscle by binding to a different cell surface receptor and, via an inhibitory G-protein, increase adenylate cyclase activity and, ultimately, cAMP, a smooth muscle relaxant.[19] Thus beta agonists should partially interfere with cholinergic-induced spasm. Cholinergic antagonists act as direct competitors for the cholinergic receptor site.

Ipratropium has a relatively slow onset of 15–30 min (compared with less than 5 min for fenoterol) and may take 1 h to reach peak effects.[20] However, ipratropium showed near-complete efficacy at 20 min after administration in a previous study in rabbits.[8] In studies in non-anaesthetized patients, 50–70% of the peak effect was usually seen by 30 min.[21]

We cannot exclude the possibility that much higher doses of ipratropium may have been more effective. Although several investigations have found that ipratropium 40–80 μg provided maximum bronchodilatation in the resting state, there is some controversy as to whether higher doses offer greater protection in induced bronchospasm.[22] One report found that ipratropium 100 μg did not prevent exercise-induced asthma but, in the same subjects, doses of 1000 μg gave significant protection.[23] Although we gave a relatively high dose, it is conceivable that doses of orders of magnitude higher might provide better protection. Such doses would require a different formulation to be practical clinically.

Another possible reason for the relative lack of effect of ipratropium is that it appears to exert its effects primarily in large airways whereas some stimuli result in mixed central and peripheral airway changes.[24] Thus beta agonists may have been more effective in treating distal changes. As the primary goal of the study was to examine the immediate effect of the drug on bronchoconstriction after intubation, the study was not extended to a longer period to examine the peak effect of ipratropium.

Our finding of significant benefit from a beta agonist delivered via a metered dose inhaler in a patient whose trachea was intubated provides useful confirmation of bench top studies. This issue is controversial, with at least one study in patients undergoing mechanical ventilation suggesting no effect on airway resistance while others have found a significant effect.[25]

The study did not have a control group because of ethical concerns about leaving patients untreated when they developed clinical signs and symptoms. A control group would have left patients untreated as a third group. Because of this lack of a control group, it is difficult to say if the decrease in resistance after ipratropium represented a true protective effect. A definitive statement would depend on knowing if a true control group would have progressed further, remained unchanged or developed spontaneous improvement.

In summary, we have demonstrated the efficacy of a beta agonist in the treatment of intubation-induced bronchoconstriction. The lesser effect of ipratropium was disappointing given the presumed cholinergic mechanisms for bronchoconstriction. We also demonstrated that even when propofol was used for induction, patients with a history of asthma were at high risk of developing an exaggerated response to tracheal intubation.

Acknowledgements

This study was supported by grant NSC83-0412-B182-009 (NMRP 345) from the National Science Council, ROC and the Office of Medical Research of the Department of Veterans Affairs of the United States

References

1 Nadel JA, Widdicombe JG. Reflex effects of upper airway irritation on total lung resistance and blood pressure. *J Appl Physiol* 1962, **17**: 861–5

2 Nadel JA, Salem H, Tamplin B, Yokiwa Y. Mechanisms of bronchoconstriction during inhalation of sulfur dioxide. *J Appl Physiol* 1965; **20**:164–7

3 Barnes PJ. Neural control of human airways in health and disease *Am Rev Respir Dis* 1986; **134**: 1289–314

4 Wu RSC, Wu KC, Wong KM, *et al.* Isoflurane anesthesia does not add to the bronchodilating effect of a beta-2-adrenergic agonist after tracheal intubation. *Anesth Analg* 1996; **83**: 238–41

5 Dueck R. Anesthesia for the asthmatic patient. *Semin Anesth* 1987; **6**: 2–9

6 Kingston HCG, Hirshman CA. Perioperative management of the patient with asthma. *Anesth Analg* 1984; **63**: 844–55

7 Allen CJ, Campbell AH. Dose response of ipratropium bromide assessed by two methods. *Thorax* 1973; **34**: 137–9

8 Wu SC, Hildebrandt J, Isner PD, Pierson DJ, Bishop MJ. Efficacy of anticholinergic and beta-adrenergic agonist treatment of maximal cholinergic bronchospasm in tracheally intubated rabbits *Anesth Analg* 1992; **75**: 777–83

9 Wright PE, Marini JJ, Bernard GR. In vitro and in vivo comparison of endotracheal tube airflow resistance. *Am Rev Respir Dis* 1989; **140**: 10–16

10 Petros AJ, Lamond CT, Bennett D. The Bicore pulmonary monitor. *Anaesthesia* 1993; **48**: 985–8

11 Yamazaki Y, Yamakage M, Ujike Y, Namiki AP. Changes in work of breathing during continuous positive airway pressure with increased airway resistance. *Chest* 1994; **105**: 860–7

12 Nathan SD, Ishaaya AM, Koerner SK, Belman MJ. Prediction of minimal pressure support during weaning from mechanical ventilation. *Chest* 1993; **103**: 1215–19

13 Wu RSC, Wu KC, Sum CW, Bishop MJ. Comparative effects of thiopental and propofol on respiratory resistance after tracheal intubation. *Br J Anaesth* 1996; **77**: 735–8

14 Eames WO, Rooke A, Wu RSC, Ryan-Dykes MA, Bishop MJ. Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. *Anesthesiology* 1996; **84**: 1307–11

15 Pizov R, Brown RH, Weiss YS, *et al.* Wheezing during induction of general anesthesia in patients with and without asthma. *Anesthesiology* 1995; **82**: 1111–16

16 Ludwig MS, Romero PV, Bates JH. A comparison of the dose–response behavior of canine airways and parenchyma. *J Appl Physiol* 1989; **67**: 1220–5

17 Wong C, Pavord I, Williams I, Britton J, Tattersfield A. Bronchodilator, cardiovascular and hypokalaemic effects of fenoterol, salbutamol and terbutaline in asthma. *Lancet* 1990; **336**: 1396–9

18 Tattersfield AE. Effect of beta-agonists and anti-cholinergic drugs on bronchial reactivity. *Am Rev Respir Dis* 1987; **136**: S64–8

19 Pakes GE, Brogdon RN, Heel RC. Ipratropium bromide. A review of its pharmacological properties and therapeutic efficacy in asthma and chronic bronchitis. *Drugs* 1980; **20**: 237–66

20 Marlin GE, Bush DE, Berend N. Comparison of ipratropium bromide and fenoterol in asthma and chronic bronchitis. *Br J Clin Pharmacol* 1978; **6**: 547–9

21 Rebuck AS, Chapman KR, Abboud R, *et al.* Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 1987; **82**: 59–64

22 Poppius H, Sovijarvi L, Tammilehto L. Controlled study on the preventing effect of inhaled ipratropium powder on asthma induced by breathing cold air during exercise. *Respiration* 1984; **46** (Suppl. 1): 45–6

23 Hartley JPR, Davies BH. Cholinergic blockade in the prevention of exercise-induced asthma. *Thorax* 1980; **35**: 680–5

24 Pierce RJ, Allen CJ, Campbell AH. A comparative study of atropine methonitrate, salbutamol and their combination in airways obstruction. *Thorax* 1979; **34**: 45–51

25 Manthous CA, Hall JB, Schmidt GA, Wood LD. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. *Am Rev Respir Dis* 1993; **148**: 1567–70

British Journal of Anaesthesia 84 (3): 363–6 (2000)

Effect of cricoid pressure on insertion of and ventilation through the cuffed oropharyngeal airway

R. M. Dravid[1]*, P. Reed[2], M. Stoneham[1] and M. T. Popat[1]

[1]Nuffield Department of Anaesthetics, Oxford Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK.
[2]Department of Anaesthetics, Milton Keynes General Hospital, Milton Keynes, Buckinghamshire, UK
*Corresponding author

We have assessed the effect of cricoid pressure on insertion of and ventilation through the cuffed oropharyngeal airway (COPA) in 53 patients, in a double-blind, randomized study. Two anaesthetists assessed adequacy of ventilation in anaesthetized and paralysed patients at the same time but using different methods. The first assessed ventilation clinically, by observing synchronized chest expansion with gentle manual ventilation and the second noted measurements of tidal volume (V_T) and peak inspiratory pressure (PIP). Five mask ventilated breaths ('baseline') were assessed as above. Patients were then allocated randomly to receive cricoid pressure (group A, n=28) or no cricoid pressure (group B, n=25). Five further mask ventilated breaths ('after manoeuvre') were again assessed. A COPA was then inserted and five further breaths ('after COPA') were assessed. A COPA was inserted at the first attempt in all patients except for one in group A who required two attempts. COPA placement was difficult in one patient in group B who had a small distance between the incisor teeth. Ventilation was clinically 'adequate' in all patients except for one in the cricoid pressure group. There were no significant differences in measured V_T or PIP between 'baseline' and 'after manoeuvre' breaths. Significant differences in V_T and PIP were found after COPA insertion in the group that received cricoid pressure, with a mean decrease in V_T of 108 ml (P=0.0049) and a mean increase in PIP of 5.2 cm H_2O (P=0.0111).

Br J Anaesth 2000; **84**: 363–6

Keywords: equipment, airway; larynx, cricoid pressure; intubation tracheal

Accepted for publication: October 21, 1999

If rapid sequence induction of anaesthesia fails, it is important to prevent regurgitation and aspiration of gastric contents while maintaining oxygenation of the patient. Since it was first described by Sellick in 1961,[1] cricoid pressure is standard practice to prevent regurgitation in these situations. Oxygenation may be maintained in the presence of continuous cricoid pressure by face mask with or without a Guedel airway, although cricoid pressure can reduce tidal volume and may cause upper airway obstruction.[2] The laryngeal mask airway (LMA) has also been used in such a situation. However, cricoid pressure impedes proper placement[3] or may reduce ease of insertion of the LMA.[4] In one study, placement of the LMA was achieved at the first attempt in only 15% of patients.[5] This is because the tip of the LMA lies behind the cricoid cartilage.[6 7] Cricoid pressure can impede ventilation through the LMA.[8] It has been recommended that the LMA should not be used when the patient's lungs can be ventilated with a face mask after failed rapid sequence induction.[3 5]

We do not know if the cuffed oropharyngeal airway (COPA) has been used when rapid sequence induction and intubation have failed, although a case of successful airway management after failed face mask ventilation has been reported.[9] The COPA is a modification of the Guedel airway which allows manual ventilation by directly connecting to the breathing system. It has a distal cuff which provides a seal in the upper pharynx behind the base of the tongue. Because the airway tip lies above the larynx, we hypothesized that continuous cricoid pressure would not interfere with placement of the COPA, and that ventilation of patients' lungs through it should be possible. In this study, we have examined the effect of cricoid pressure on insertion of and subsequent ventilation through the COPA.

Patients and methods

After obtaining approval from the Local Ethics Committee and written informed consent, we studied 53 ASA I or II patients, aged 20–70 yr, undergoing elective gynaecological surgery with tracheal intubation (Table 1). Patients with any pathology of neck or upper respiratory tract, or who were considered at risk of aspiration of gastric contents

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Patient characteristics (mean (SD or range) or median [range]) in groups A (cricoid pressure) and B (no cricoid pressure)

Variable	**Group A (*n* = 28)**	**Group B (*n* = 25)**
Age (yr)	40 6 (26–65)	37.2 (24–68)
Height (m)	1.61 (0 06)	1 64 (0 06)
Weight (kg)	69.5 (16.1)	69.5 (9.9)
Body mass index (kg m^{-2})	26.7 (6.2)	26 2 (4 0)
Mallampati score	2 [1–4]	1 [1–4]
Cormack and Lehane score	1 [1–3]	2 [1–3]

were excluded. Patients were premedicated with temazepam 20 mg orally. The ECG and oxygen saturation were monitored continuously, arterial pressure was recorded non-invasively and a peripheral nerve stimulator was used to monitor neuromuscular block.

At the start of the operating session and before each anaesthetic, the anaesthetic nurse practised cricoid pressure by applying force with fingers on a weighing scale to obtain a reading of 3 kg.[10] The patient was placed in the Magill intubating position. After preoxygenation, anaesthesia was induced with midazolam 2.5 mg, fentanyl 1.5 µg kg^{-1} and propofol 1.5–2.5 mg kg^{-1}. Rocuronium 0.6 mg kg^{-1} was administered and the patient's lungs were ventilated manually by mask with 1.2% isoflurane in oxygen. A Datex-Engstrom spirometry monitor (Helsinki, Finland) incorporating a D-lite reusable sensor was used to measure expired tidal volume (V_T) and peak inspiratory pressure (PIP).

Two anaesthetists took part in the study. The first undertook mask ventilation, insertion of a COPA and clinically assessed chest movement as 'adequate' or 'inadequate' by observing expansion of the chest with gentle bag ventilation. Ventilation was judged adequate if chest expansion was obvious. The second anaesthetist recorded V_T and PIP from the monitor. The anaesthetists made their recordings simultaneously for the same breaths, but did not communicate each others findings. After confirming that neuromuscular block was complete, three sets of readings for five breaths each were recorded, as described below.

The first anaesthetist delivered five breaths by mask ('baseline'). Patients were allocated randomly to one of two groups by computer-generated random numbers. Patients in group A received bimanual cricoid pressure, while those in group B did not. Cricoid pressure was applied by a right-handed nurse standing on the right side of the patient with the left hand supporting the neck from behind. A green drape was used on the neck as a screen to blind the anaesthetists as to whether or not cricoid pressure was being applied, but allowed a clear, unobstructed view of the chest. Even when cricoid pressure was not applied, the hands of the anaesthetic nurse were similarly positioned under cover of the screen. The first anaesthetist removed his hand and face mask from the patient's face after delivering the five 'baseline' breaths and replaced it only after the anaesthetic nurse had started the 'manoeuvre' under cover of the drapes, ensuring that he remained blind to the manoeuvre. After this, five further mask ventilated breaths were measured ('after manoeuvre'). Direct laryngoscopy was then performed and the laryngeal view recorded according to the criteria of Cormack and Lehane.[11] After this, a pre-selected, lubricated COPA was inserted. The size of the device was determined by a method described previously.[12] After COPA insertion, five further breaths were evaluated ('after COPA'). The size, time for insertion (from start of insertion to inflation of the cuff of the COPA), number of attempts at insertion and any other problems were recorded. The device was replaced with the next biggest size if there was a big leak despite cuff inflation with up to 10 ml more than that recommended by the manufacturer or if chest expansion was not considered clinically adequate. If at any time oxygen saturation decreased to less than 95%, the study was discontinued and ventilation then labelled as 'failed'. At the end of the study, the anaesthetic nurse immediately revalidated blindly, the force used for cricoid pressure on a weighing scale.

Table 2 COPA insertion and cricoid pressure data (mean (SD)) in groups A (cricoid pressure) and B (no cricoid pressure) No significant differences

Variable	**Group A (*n* = 28)**	**Group B (*n* = 25)**
Insertion time (s)	25 (12)	22 (5)
Force at cricoid cartilage (kg)	3.24 (0 42)	3 15 (0 35)

We considered that a reduction of tidal volume by 100 ml would be clinically significant. In a small pilot study and in other published work,[2] the SD of tidal volume during manual ventilation through a COPA was estimated as 120 ml. Using a nomogram for power calculations, at least 25 patients were required in each group for a power of 0.8 at the 5% significance level.

Statistical analysis

Data were analysed using Stat View for Windows version 4.53 (Abacus Concepts Inc., California, USA). Data concerning COPA insertion were analysed using an unpaired *t* test. Inter-patient variability in V_T and PIP was analysed using two-way analysis of variance (ANOVA). Analysis of the effects of cricoid pressure on V_T and PIP before and after COPA insertion was performed by ANOVA using the median value of each of the five observations.

Results

There were no differences between the two groups in the time required for COPA insertion or the force applied for cricoid pressure (Table 2).

The COPA was inserted at the first attempt in all patients, with the exception of one patient in group A (cricoid group) who required two attempts. There were no difficulties in introducing the COPA into the mouth, turning it through 180° to point the tip caudad, placing it down to its final position or strapping and inflation in any patient except for one in group B (no cricoid pressure). This patient had a

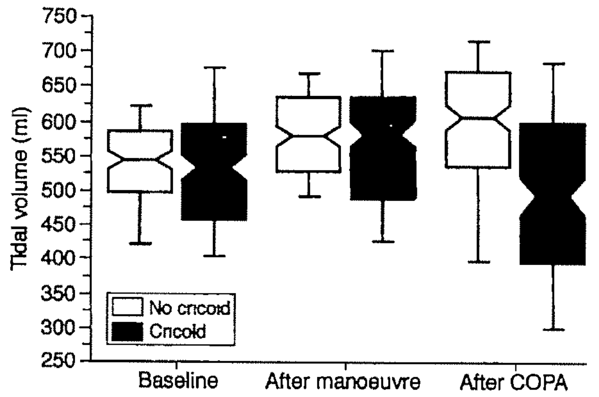


Fig 1 Box and whisker plots of median expired tidal volume for 'baseline', 'after manoeuvre' and 'after COPA' set of breaths The box indicates the lower and upper quartiles (25 and 75 percentiles) and the central line is the median, the points on the whiskers next to central line represent 95% CI, and the bars at the end of the 'whiskers' are 10% and 90% values.

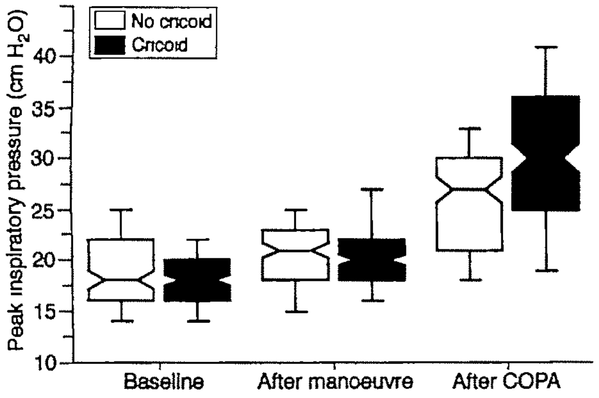


Fig 2 Box and whisker plots of median peak inspiratory pressure for 'baseline', 'after manoeuvre' and 'after COPA' set of breaths. The box indicates the lower and upper quartiles (25 and 75 percentiles) and the central line is the median; the points on the whiskers next to central line represent the 95% CI; and the bars at the end of the 'whiskers' are 10% and 90% values

narrow inter-incisor distance, a Mallampati class IV airway and a Cormack and Lehane view of 3 at laryngoscopy. When the device was in place, ventilation was judged clinically to be adequate. In all patients, the lungs were ventilated adequately, as assessed clinically, except in one patient in group A. Oxygen saturation in this patient decreased to less than 95% and ventilation was labelled failed.

In three patients in group A, an audible leak persisted after inflation of the COPA cuff with 10 ml more than that recommended by the manufacturer. In all of these patients, the next biggest size COPA was inserted successfully and ventilation was judged as adequate. There were no significant intra-patient differences between the five observations for V_T or PIP for each patient (ANOVA). Median values for each set of five observations are displayed as box and whisker plots in Figures 1 and 2. There were no significant differences for V_T or PIP between 'baseline' and 'after manoeuvre' sets of mask ventilated breaths in both groups. After a COPA was inserted, V_T decreased and PIP increased significantly, by mean values of 108 ml (P=0.0049) and 5.2 cm H_2O (P=0.0111), respectively, in those who received cricoid pressure.

Discussion

Different airway devices, including the Guedel airway and LMA, have been tried to facilitate ventilation in the presence of cricoid pressure.[2-5] However, none has proved to be entirely satisfactory in meeting the criteria of successful insertion and maintenance of adequate ventilation in the presence of continuous cricoid pressure. In our study, we have shown that a COPA can be inserted successfully in the presence of continuous cricoid pressure. Successful insertion of a COPA was achieved at the first attempt in all patients except for one in the cricoid pressure group who required two attempts. In this patient, the COPA slipped out after cuff inflation and was reinserted successfully

Allman reported significant reductions in tidal volume and increased airway pressure in patients whose lungs were ventilated by mask (with or without a Guedel airway) when continuous cricoid pressure was applied.[2] We found no significant changes in tidal volume or airway pressures with mask ventilation before and after application of cricoid pressure. We did not use a Guedel airway to assist mask ventilation. In Allman's study, cricoid pressure was not standardized and an excessive force during its application could have been responsible for the increase in airway pressures and upper airway obstruction. We standardized the force applied, as described by Vanner and colleagues,[10] and then observed its effect on mask ventilation and on the use of the COPA. Two anaesthetic nurses who work routinely in the obstetric theatres took part in the study. They conscientiously practised cricoid pressure by producing a force of 3 kg equivalent to 30 Newtons on a weighing scale before each case and revalidated it each time afterwards by reproducing the same force with an independent observer recording the reading on the scale. This may explain why none of our patients had airway obstruction.

Although single-handed cricoid pressure is as effective as bimanual pressure,[13] we used bimanual cricoid pressure in our study. During our pilot study we found that single-handed cricoid pressure interfered with extension of the head and neck, opening of the mouth, turning the COPA in the mouth through 180° and placing it in its final position; insertion was easier and ventilation successful when bimanual cricoid pressure was applied. Bimanual cricoid pressure is recommended during rapid sequence induction.[14]

Placement of the LMA and subsequent ventilation have been shown to be impaired by cricoid pressure.[5 8] Some recommend that cricoid pressure should be released transiently to facilitate insertion,[4 5] but this may allow regurgitation and aspiration. Subsequent ventilation may also be difficult when cricoid pressure is reapplied[8] Cricoid pressure is less likely to interfere with placement of a COPA and ventilation through it. We assessed ventilation clinically by observing chest expansion when the lungs were ventilated manually and simultaneously recorded V_T and PIP for the same breaths. Ventilation appeared adequate in all patients except for one in the cricoid pressure group. This patient's lungs could not be ventilated after insertion of a COPA because of a major leak that could not be prevented by further cuff inflation. Before the anaesthetist could change the device, oxygen saturation decreased rapidly to less than 95% and therefore the study was discontinued and ventilation labelled as failed.

The significant reduction in tidal volume recorded after insertion of a COPA in patients who received cricoid pressure could have been caused by a leak around the cuff of the device, which we did not measure. PIP increased significantly after COPA insertion only in the group that received cricoid pressure.

Using fibreoptic visualization, Brimacombe suggested that the anterior tilt of the larynx caused by cricoid pressure can approximate the vocal cords and thus some degree of airway obstruction.[15] We are unable to offer an explanation for the increase in PIP as we did not investigate this using a fibreoptic scope.

In summary, we have shown that placement of a COPA and clinically effective ventilation through it is possible in the presence of continuous cricoid pressure. We are however, unable to recommend its routine clinical use in a failed rapid sequence induction scenario until further work is undertaken to explain the changes in tidal volume and airway pressures.

Acknowledgement

We thank Dr John Moyle and Dr Eileen Palayiwa for valuable suggestions in the physical measurements and Dr John Sear for statistical analysis

References

1 Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; **2**: 404–6

2 Allman KG. The effect of cricoid pressure application on airway patency. *J Clin Anesth* 1995; **7**: 197–9

3 Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure impedes placement of the laryngeal mask airway. *Br J Anaesth* 1995; **74**: 521–5

4 Brimacombe J, White A, Berry A. Effect of cricoid pressure on ease of insertion of the laryngeal mask airway. *Br J Anaesth* 1993; **71**: 800–2

5 Ansermino JM, Blogg CE. Cricoid pressure prevents insertion of laryngeal mask airway. *Br J Anaesth* 1992; **69**: 465–6

6 Brain AIJ. The development of the laryngeal mask—a brief history of the invention, early clinical studies and experimental work from which the laryngeal mask evolved. *Eur J Anaesthesiol* 1991; (Suppl. 4): 5–17

7 Brain AIJ. Laryngeal mask misplacement—causes, consequences and solutions. *Anaesthesia* 1992; **47**: 531–2

8 Asai T, Barclay K, McBeth C, Vaughan RS. Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation. *Br J Anaesth* 1996; **76**: 772–6

9 Asai T, Koga K, Stacey MRW. Use of the cuffed oropharyngeal airway after difficult ventilation through a facemask. *Anaesthesia* 1997; **52**: 1236–7

10 Vanner RG, Clarke P, Moore WJ, Raftery S. The effect of cricoid pressure and neck support on the view at laryngoscopy. *Anaesthesia* 1997; **52**: 896–900

11 Cormack RS, Lehane J Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–11

12 Dravid RM, Popat MT. The cuffed oropharyngeal airway. *Anaesthesia* 1999; **54**: 402

13 Asai T, Barclay K, Power I, Vaughan RS. Cricoid pressure and the LMA: efficacy and interpretation. *Br J Anaesth* 1994; **73**: 863–4

14 Yentis SM. The effects of single-handed and bimanual cricoid pressure on the view at laryngoscopy. *Anaesthesia* 1997; **52**: 332–5

15 Brimacombe J. Cricoid pressure and the laryngeal mask airway. *Anaesthesia* 1991; **46**: 986–7

British Journal of Anaesthesia **84** (3) 367–71 (2000)

Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials

E. Ernst* and M. H. Pittler

Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, 25 Victoria Park Road, Exeter EX2 4NT, UK

**Corresponding author*

Ginger (*Zingiber officinale*) is often advocated as beneficial for nausea and vomiting. Whether the herb is truly efficacious for this condition is, however, still a matter of debate. We have performed a systematic review of the evidence from randomized controlled trials for or against the efficacy of ginger for nausea and vomiting. Six studies met all inclusion criteria and were reviewed. Three on postoperative nausea and vomiting were identified and two of these suggested that ginger was superior to placebo and equally effective as metoclopramide. The pooled absolute risk reduction for the incidence of postoperative nausea, however, indicated a non-significant difference between the ginger and placebo groups for ginger 1 g taken before operation (absolute risk reduction 0.052 (95% confidence interval −0.082 to 0.186)). One study was found for each of the following conditions: seasickness, morning sickness and chemotherapy-induced nausea. These studies collectively favoured ginger over placebo.

Br J Anaesth 2000; **84**: 367–71

Keywords: pharmacology, ginger; vomiting, nausea; vomiting, incidence; research, emesis; clinical trials

Accepted for publication: September 1, 1999

Ginger (*Zingiber officinale*) has been used for medicinal purposes since antiquity. In particular, it has been an important plant for the traditional Chinese and Indian pharmacopoeia. One of its indications has always been the treatment of nausea and vomiting. The aromatic, spasmolytic carminative and absorbent properties of ginger suggest that it has direct effects on the gastrointestinal tract.[1] German and European monographs on ginger are available[2 3] and both list nausea/vomiting as indications. Recently, the US pharmacopoeia has approved ginger and powdered ginger monographs for inclusion in the National Formulary.[4]

The notion that ginger may be effective for nausea and vomiting is supported by several lines of evidence. Animal experiments suggest that ginger has antiemetic activity[5] when nausea is induced by cisplatin[6] or cyclophosphamide.[7] Studies in healthy human volunteers suggest that ginger reduces experimentally induced nausea.[8 9] Furthermore, non-randomized, non-placebo-controlled studies suggest an antiemetic effect in human patients.[10 11] However, these data are insufficient to evaluate whether or not ginger is truly efficacious for clinical nausea and vomiting.

In this study, we have assessed the available evidence from randomized, controlled trials (RCT) for or against the efficacy of ginger for clinical nausea and vomiting.

Methods

Systematic literature searches were performed to identify all RCTs on ginger for nausea and vomiting. Computerized literature databases were Medline, Embase, Biosis, CISCOM (Research Council for Complementary Medicine, London) and the Cochrane Library (all from their respective inception to November 1997). The search terms used were ginger, *Zingiber officinale* and Ingwer (German term for *Zingiber officinale*). A manual search was performed using the bibliographies of studies and reviews located through the computer search and through scanning our own files. In addition, manufacturers of ginger preparations were asked to contribute published and unpublished material. No language restrictions were imposed.

Only double-blind, placebo-controlled RCTs of ginger monopreparations for nausea and vomiting were included. Studies on experimentally induced nausea or vomiting, or both, were excluded. All studies were assessed independently by both authors. Data were extracted in a standardized, predefined manner. The methodological quality of each study was assessed using the scoring system developed by Jadad and colleagues.[12] The authors met to agree consensus on the assessed data Disagreements were settled by discussion.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Statistical combination of data was performed for studies on postoperative nausea. The incidence of postoperative nausea was defined as the common end-point and used to assess differences between treatment and control intervention. The absolute risk reduction and 95% confidence intervals were calculated using standard meta-analysis software (RevMan 3.01, Cochrane Collaboration). The number-needed-to-treat was calculated as the inverse of the absolute risk reduction.[13 14]

Results

Six studies met all of our criteria and were reviewed.[15–20] The assessment of methodological quality revealed a score of at least 3 of 5 points in the majority of studies. The studies related to four different clinical conditions: seasickness, morning sickness, chemotherapy-induced nausea and postoperative nausea. Most were conducted on postoperative nausea.[18–20] Key data are summarized in Table 1.

Grøntved and colleagues[15] studied 80 Danish cadets, allocated randomly to receive either one dose of ginger powder 1 g or placebo. Symptoms of seasickness were evaluated during the subsequent 4 h. Volunteers who received ginger powder suffered less seasickness compared with those who received placebo. The difference between ginger powder and placebo was statistically significant ($P<0.05$) 4 h after receiving the medication.

Fischer-Rasmussen and colleagues[16] conducted a small crossover study in 27 women suffering from hyperemesis gravidarum. Patients received ginger powder 250 mg or placebo, four times daily for 4 days. Sickness was assessed using a symptom score. The results suggested a significantly ($P<0.05$) greater symptomatic benefit after administration of ginger compared with placebo.

One RCT was identified for chemotherapy-induced nausea.[17] Forty-one patients suffering from leukaemia were allocated randomly to one of two groups to receive either oral ginger or placebo, after administration of compazine i.v. The results suggested a significant (*P* value not reported) reduction in nausea in patients who received ginger compared with those who received placebo. This study has only been published as an abstract and crucial details were not reported.

Bone and colleagues[18] studied 60 women before major gynaecological operations. Patients were allocated randomly to receive ginger 1 g, metoclopramide 10 mg or placebo as a single dose given with preoperative medication. The severity of postoperative nausea was assessed on a four-point scale. The incidence of nausea during the first 24 h after surgery was 28%, 30% and 51% in the ginger, metoclopramide and placebo groups, respectively. A statistically significant ($P<0.05$) difference in favour of ginger compared with placebo was reported for the total number of incidents of nausea.

Phillips, Hutchinson and Ruggier[19] randomized 120 women before laparoscopic surgery to one of three similar treatment groups. The medication was given 1 h before surgery and the incidence of nausea and vomiting was 21%, 27% and 41% in the ginger, metoclopramide and placebo groups, respectively. Significantly ($P=0.006$) fewer patients with nausea were reported in the ginger group compared with the placebo group.

In a study by Arfeen and colleagues,[20] 108 women were allocated randomly to receive ginger 0.5 g, ginger 1 g or placebo before laparoscopic surgery. The incidence of nausea and vomiting was monitored 3 h after operation. There were no significant differences between groups.

Data from RCT on postoperative nausea[18–20] were suitable for statistical pooling. The pooled absolute risk reduction for the incidence of postoperative nausea indicated a non-significant difference between the ginger group treated with ginger 1 g before operation and the placebo group (absolute risk reduction 0.052 (95% confidence interval −0.082 to 0.186)). These values indicate a point estimate of the number-needed-to-treat of 19 and a 95% confidence interval which also includes the possibility of no benefit.[21]

Discussion

The majority of the studies reported that ginger powder 1 g daily alleviated clinical nausea of diverse causes. One study on postoperative nausea,[20] however, showed no significant beneficial effects of ginger compared with placebo and, indeed, between doses of 0.5 g and 1 g of ginger powder. This study is also the most rigorous on this indication. The discrepancy between this negative outcome and the positive results from other RCT is not readily explicable.

There are only few data on the actions of ginger. Gingerols, in particular 6-gingerol, have been identified as the active ingredient of ginger, and are also responsible for its characteristic taste. There are several mechanisms which could explain the possible antiemetic effects of ginger. In an animal model, for instance, it was demonstrated that 6-gingerol enhanced gastrointestinal transport.[22] This and other compounds of ginger have also been shown to have anti-hydroxytryptamine activity in isolated guineapig ileum.[23 24] Galanolactone, another constituent of ginger, is a competitive antagonist at ileal 5-HT$_3$ receptors.[24] Thus antiemesis could be brought about by effects on the gastric system through 5-HT$_3$ antagonism. This hypothesis is weakened by the results of a randomized, placebo-controlled, crossover study in human volunteers reporting that oral ingestion of powdered ginger root did not affect gastric emptying rate.[25] In contrast, effects on the central nervous system may be involved. This notion is strengthened by the finding that, in an animal model, oral 6-gingerol prevented vomiting in response to cyclophosphamide.[7] A central effect is also implicated by studies reporting that ginger partly prevents motion sickness symptoms in healthy human volunteers.[8–9] Another study investigating motion sickness, however, reported no effects of ginger on the vestibular and oculomotor system.[26]

Table 1 Double-blind, randomized controlled trials of ginger for clinical nausea and vomiting

First author (year), indication	Quality score[12] (max 5)	Patient sample	Design	Treatment	Control	Duration of treatment	Outcome measure	Result	Comment
Grøntved[15] (1988), seasickness	4	80 cadets	2 parallel groups	Ginger powder 1 g	Placebo	One dose only	Symptom scores during 4 h after medication	Ginger superior to placebo but significant ($P<0.05$) only after 4 h	5 subjects in the placebo group vomited 2 or more times, compared with none in the verum group
Fischer-Rasmussen[16] (1990), morning sickness	3	30 pregnant women with severe nausea	Cross-over, 2-day wash-out period	Ginger powder 4 × 250 mg daily	4 × placebo capsules daily	4 days	Symptom score	Significantly (P = 0.035) greater relief with ginger compared with placebo	3 drop outs; one spontaneous abortion occurred in the 12th week of gestation
Pace[17] (1987), chemotherapy-induced nausea	2	41 patients receiving chemotherapy (compazine) for leukaemia	2 parallel groups	Ginger (no further details)	Placebo (no further details)	2 days	Nausea symptoms	Significantly (P value not reported) less severe nausea in ginger compared with placebo group	Only published as an abstract, important details are missing
Bone[18] (1990), postoperative nausea	3	60 women after major gynaecological surgery	3 parallel groups	Ginger 1 g orally at time of premedication	Placebo or metoclopramide (10 mg)	One dose before operation	Incidence and severity of nausea	Incidence of nausea. 28% ginger, 51% placebo, 30% metoclopramide	Nausea was more severe in the placebo group throughout the 24-h observation period
Phillips[19] (1993), postoperative nausea	3	120 women after laparascopic gynaecological surgery	3 parallel groups	Ginger powder 1 g	Placebo or metoclopramide (10 mg)	One dose 1 h before anaesthesia	Incidence of nausea and vomiting	Incidence rates were 21% ginger, 41% placebo, 27% metoclopramide	No side-effects were observed, less patients from ginger group needed antiemetics subsequently
Arfeen[20] (1995), postoperative nausea	4	108 women after laparascopic gynaecological surgery	3 parallel groups	Ginger 0.5 or 1 g 1 h before surgery	Placebo	One dose before operation	Incidence of nausea and vomiting	No significant inter-group differences	Sample size determined by power calculation, there was a non-significant trend for high-dose ginger to increase nausea and vomiting

With a herb commonly used as a foodstuff and spice, one is inclined to assume that it is free of serious adverse effects. However, this can be a dangerous fallacy.[27] For instance, in doses taken with food, a spice may be safe, yet when taken in higher doses as a drug, this might not apply. There were no reports of adverse reactions to ginger compared with placebo in any of the above studies. The British Herbal Compendium documents no adverse effects of ginger.[28] The German monograph[2] warns that ginger should not be taken during pregnancy. The caution is based on data suggesting that ginger is mutagenic in several test systems.[29–31] However, the situation is complex and antimutagenic effects have also been reported.[32] Systematic studies of ginger or its constituents in mammalian cell cultures have not been reported. There is also no evidence that ginger is harmful when taken by pregnant women.[16] However, in the light of suspicion of mutagenicity it seems wise to err on the side of caution.

Publication bias is of concern for all systematic reviews which may lead to a false positive overall result. It is known that negative studies tend to remain unpublished.[33] The literature relating to complementary medicine could be particularly distorted.[34] The data available are by no means beyond criticism. The outcome measures used in the above trials may be of debatable reliability, sample sizes are usually small and power calculations are mostly lacking.

Modern antiemetic agents include droperidol, the prokinetic metoclopramide and the 5-HT$_3$ receptor antagonist odansetron.[35] The latter is superior to placebo and comparative studies demonstrated no significant differences compared with droperidol or metoclopamide.[36] In comparative studies of ginger and metoclopramide,[18 19] no significant difference was found between treatments.

In summary, we found that ginger is a promising antiemetic herbal remedy, but the clinical data to date are insufficient to draw firm conclusions. Further rigorous studies are needed to establish whether ginger is efficacious for clinical nausea and vomiting.

References

1 Tyler VE. Some recent advances in herbal medicine. *Pharm Int* 1986; **7**: 203–7

2 Kommission E. Monographie Zingiberis rhizoma. Bundesanzeiger, 1988; Nr 85, 5.5

3 ESCOP Monograph. Zingiberis rhizoma (Ginger). Europ Scientific Coop Phytotherapy. Elburg, 1996

4 USP adopts ginger monograph. *Herbalgram* 1997; **41**: 12

5 Frisch C, Hasenohrl RU, Mattern CM, Hacker R, Huston JP. Blockage of lithium chloride-induced conditioned place aversion as a test for antiemetic agents: comparison of metoclopramide with combined extracts of *Zingiber officinale* and *Ginkgo biloba*. *Pharmacol Biochem Behav* 1995; **52**: 321–7

6 Sharma SS, Kochupillai V, Gupta SK, Seth SD, Gupta YK. Antiemetic efficacy of ginger (Zingiber officinale) against cisplatin-induced emesis in dogs. *J Ethnopharmacol* 1997; **57**: 93–6

7 Yamahara J, Rong HQ, Naitoh Y, Kitani T, Fujimura H. Inhibition of cytotoxic drug-induced vomiting in suncus by a ginger constituent *J Ethnopharmacol* 1989; **27**: 353–5

8 Mowrey DB, Clayson DE. Motion sickness, ginger and psychophysics. *Lancet* 1982; **i**: 655–6

9 Grøntved A, Hentzer E. Vertigo-reducing effect of ginger root. A controlled clinical study. *J Otorhinolaryngol Relat Spec* 1986; **48**: 282–6

10 Meyer K, Schwartz J, Crater D, Keyes B. Zingiber officinale (ginger) used to prevent 8-mop associated nausea. *Dermatol Nurs* 1995; **7**: 242–4

11 Schmid R, Schick T, Steffen R, Tschopp A, Wilk T. Comparison of seven commonly used agents for prophylaxis of seasickness. *J Travel Med* 1994; **1**: 203–6

12 Jadad AR, Moore RA, Carrol D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12

13 Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995; **310**: 452–4

14 Moore A, McQuay H. Calculating NNTs. *Bandolier* 1997; **36**: 2

15 Grøntved A, Brask T, Kambskard J, Hentzer E. Ginger root against seasickness: A controlled trial on the open sea. *Acta Otolaryngol* 1988; **105**: 45–9

16 Fischer-Rasmussen W, Kjær SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 1990; **38** 19–24

17 Pace JC. Oral ingestion of encapsulated ginger and reported self-care actions for the relief of chemotherapy-associated nausea and vomiting. *Dissertations Abstracts Int* 1987; **47**: 3297-B

18 Bone ME, Wilkinson DJ, Young JR, McNeil J, Charlton S. Ginger root–a new antiemetic: The effect of ginger root on postoperative nausea and vomiting after major gynaecological surgery. *Anaesthesia* 1990; **45**: 669–71

19 Phillips S, Ruggier R, Hutchinson SE. Zingiber officinale (Ginger)–an antiemetic for day case surgery. *Anaesthesia* 1993; **48**: 715–17

20 Arfeen Z, Owen H, Plummer JL, Ilsley AH, Sorby-Adams RAC, Doecke LJ. A double-blind randomized controlled trial of ginger for the prevention of postoperative nausea and vomiting. *Anaesth Intensive Care* 1995; **23**: 449–52

21 McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med* 1997; **126**: 712–20

22 Yamahara J, Huang QR, Li Y, Xu L, Fujimura H. Gastrointestinal motility enhancing effect of ginger and its active constituents. *Chem Pharm Bull (Tokyo)* 1990; **38**: 430–1

23 Yamahara J, Huang QR, Iwamoto M, Kobayashi G, Matsuda H, Fujimura H. Active components of ginger exhibiting anti-serotinergic action. *Phyto Res* 1989; **3**: 70–1

24 Huang Q, Iwamoto M, Aoki S, *et al.* Anti-5-hydroxytryptamine$_3$ effect of galanolactone, diterpenoid isolated from ginger. *Chem Pharm Bull (Tokyo)* 1991; **39**: 397–9

25 Phillips S, Hutchinson S, Ruggier R. Zingiber officinale does not affect gastric emptying rate A randomised, placebo-controlled, crossover trial. *Anaesthesia* 1993; **48**: 393–5

26 Holtmann S, Clarke AH, Scherer H, Hohn M. The anti-motion sickness mechanism of ginger. A comparative study with placebo and dimenhydrinate. *Acta Otolaryngol (Stockh)* 1989; **108**: 168–74

27 Ernst E, De Smet PAGM, Shaw D, Murray V. Traditional remedies and the test of time. *Eur J Clin Pharmacol* 1998; **54**: 99–100

28 Bradley P, ed. *British Herbal Compendium*. Bournemouth: British Herbal Medical Association, 1990

29 Abraham S, Abraham SK, Radhamony G. Mutagenic potential of the condiments, ginger and turmeric. *Cytologia* 1976; **41**: 591–5

30 Nagabhushan M, Amonkar AJ, Bhide SV. Mutagenicity of gingerol and shogaol and antimutagenicity of zingerone in salmonella/microsome assay. *Cancer Lett* 1987; **36**: 221–33

31 Soudamini KK, Unnikrishnan MC, Sukumaran K, Kuttan R. Mutagenicity and anti-mutagenicity of selected spices. *Indian J Physiol Pharmacol* 1995; **39**: 347–53

32 Corrigan D. Zingiber officinale. In: De Smet PAGM, Keller K, Hansel R, Chandler RF, eds. *Adverse Effects of Herbal Drugs*, vol. 3. Berlin: Springer Berling, 1997; 215–28

33 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**: 867–72

34 Ernst E, Pittler MH. Alternative therapy bias. *Nature* 1997; **385**: 480

35 Baines MJ. Nausea, vomiting and intestinal obstruction *BMJ* 1997; **315**. 1148–50

36 Tramèr MR, Moore RA, Reynolds DJM, McQuay HJ. A quantitative systematic review of odansetron in treatment of established postoperative nausea and vomiting. *BMJ* 1997; **314**. 1088–92

British Journal of Anaesthesia 84 (3): 372–7 (2000)

BJA

LABORATORY INVESTIGATION

Effects of halothane on respiratory mechanics and lung histopathology in normal rats

G. S. Reta[1], J. A. Riva[1], H. Piriz[1], A. S. Medeiros[2], P. R. M. Rocco[2] and W. A. Zin[2]*

[1]Departamento de Fisiopatología, Universidad de la República, Montevideo, Uruguay. [2]Federal University of Rio de Janeiro, Carlos Chagas Filho Biophysics Institute and Thoracic Disease Institute, Ilha do Fundão, 21949-900, Rio de Janeiro, RJ, Brazil

**Corresponding author: Universidade Federal do Rio de Janeiro, Instituto de Biofísica Carlos Chagas Filho, Centro de Ciências da Saúde, 21949-900, Rio de Janeiro, RJ, Brazil*

It is generally accepted that halothane reduces airway and tissue resistance in lungs with pre-existing airway tone. However, under conditions of resting airway tone, pulmonary resistance remains unaltered. In this study, we have determined the effects of halothane on respiratory system, pulmonary and chest wall resistive, elastic and viscoelastic mechanical properties, and related the results to findings from lung histology in intact normal rats. Sixteen adult male Wistar rats were allocated randomly to one of two groups (n=8 in each group): control or halothane group. In the control group, animals were sedated with diazepam 5 mg i.p. and anaesthetized with pentobarbital 20 mg kg^{-1} i.p. In the halothane group, the anaesthetic was administered at an end-tidal concentration of 1 MAC throughout the study. Rats were paralysed and underwent mechanical ventilation. Halothane decreased airway resistance but increased the tissue component of resistance (caused by viscoelastic elements and lung inhomogeneity). Static and dynamic elastance also increased with halothane anaesthesia. Pulmonary resistance remained unchanged. Lung histopathology demonstrated airway dilatation and a greater degree of lung collapse and hyperinflation in the halothane group. We conclude that halothane anaesthesia acts both on airway and lung tissue. In airway tissue, dilatation occurs but the lung periphery stiffens. Consequently, these opposing effects result in no overall apparent change in mechanical properties, although changes are observed during halothane anaesthesia in normal animals and subjects.

Br J Anaesth 2000; **84**: 372–7

Keywords: lung, mechanics; lung, histology; anaesthetics volatile, halothane; rat

Accepted for publication: October 22, 1999

Halothane is a volatile anaesthetic agent which can decrease high pulmonary resistance caused by stimulation of the vagus nerves or by administration of methacholine, histamine or specific allergens.[1–3] This attenuation is believed to be caused by bronchodilatation and decreased tissue resistance.[3 4] However, in some reports, halothane had no effect on basal resistance or compliance of the lungs in the absence of active smooth muscle tone.[5 6] These discrepancies on respiratory mechanics in animals with normal airway tone could result from: (a) comparison of isolated with intact preparations, (b) variability in lung volume, (c) simultaneous use of more than one anaesthetic agent and (d) diversity of methods used for determining lung resistance. In this study, respiratory system, lung and chest wall mechanical properties were subdivided into resistive, elastic and viscoelastic components during halothane anaesthesia in normal rats, to define the sites of action of this anaesthetic agent. In addition, lung histology was performed to support the physiological findings.

Materials and methods

All animals received humane care in compliance with the 'Principles of Laboratory Animal Care' formulated by the National Society for Medical Research and the 'Guiding Principles in the Care and Use of Animals' approved by the Council of the American Physiological Society, USA.

The experiments were performed in two groups of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

isogenic adult male Wistar rats. In the first group (control) (n=8, mean body weight 305 (SD 4) g; range 300–310 g), rats were sedated with diazepam 5 mg i.p. and anaesthetized with pentobarbital 20 mg kg^{-1} i.p. In the second group (halothane) (n=8, mean body weight 299 (8) g; range 290–310 g), animals were anaesthetized with 1 MAC (0.95±0.02%) of halothane. Halothane was administered via a vaporizer (Flu-o-Pen, Narcosul, Porto Alegre, Brazil) through which a flow of air was passed. A tightly fitting cannula (1.5 mm id) was introduced into the trachea through a tracheotomy. Halothane was then delivered to the animal using a T-piece system attached to the tracheal cannula. There was no appreciable change in tracheal pressure. Anaesthesia was maintained throughout the experiment at stage III, assessed by pupil size and position, response to light, position of the nictitating membrane and tone of the jaw muscles. All animals were placed in the supine position on a surgical table.

A pneumotachograph (1.5 mm id, length 4.2 cm, distance between side ports 2.1 cm)[7] was connected to the tracheal cannula for measurements of airflow ($\dot{V}$) and changes in lung volume (V). The pressure gradient across the pneumotachograph was determined using a Validyne MP45-2 differential pressure transducer (Northridge, CA, USA). The flow resistance of the equipment (tracheal cannula included) was constant up to flow rates of 26 ml s^{-1} (well above the inspiratory flow used in the present experiments, see below), and was 0.003 kPa ml^{-1} s. Equipment resistive pressure ($=\text{Req}.\dot{V}$) was subtracted from respiratory system and pulmonary resistive pressures so that our results represented intrinsic values, assuming that the upper airways were bypassed. Because abrupt changes in diameter were not present in our circuit, errors of measurement of flow resistance were avoided[8] The equipment deadspace was 0.4 ml. Tracheal pressure (Ptr) was measured at the side port of the tracheal cannula with a Hewlett-Packard 270 differential pressure transducer (Waltham, MA, USA). Changes in oesophageal pressures (Pes), which reflect chest wall pressure (Pw), were measured with a 30-cm long water-filled catheter (PE205) with side holes at the tip connected to a PR23-2D-300 Statham differential pressure transducer (Hato Rey, Puerto Rico). The catheter was passed into the stomach and then slowly withdrawn into the oesophagus. Correct positioning was assessed using the occlusion test.[9] This test compares ΔPes and ΔPtr during spontaneous inspiratory efforts subsequent to airway occlusion at end-expiration. In all instances, ΔPes was close to ΔPtr; the difference did not exceed 3%. The frequency responses of Ptr and Pes measurement systems were level up to 20 Hz, without appreciable phase shift between the signals. All signals were conditioned and amplified in a Beckman type R Dynograph (Schiller Park, IL, USA). Flow and pressure signals were also passed through 8-pole Bessel filters (902LPF, Frequency Devices, Haverhill, MA, USA) with corner frequency set at 100 Hz, sampled at 200 Hz with a 12-bit analogue-to-digital converter (DT-2801A, Data Translation, Marlboro, MA, USA), and stored on a microcomputer. All data were collected using LABDAT software (RHT-InfoDat Inc., Montreal, Quebec, Canada).

Neuromuscular block was achieved with gallamine triethyliodide 2 mg kg^{-1} i.v., and artificial ventilation was provided by a Salziner constant flow ventilator (Instituto do Coração–USP, São Paulo, SP, Brazil). During the test breaths, a 5-s end-inspiratory pause was generated by adjusting the ventilator settings, whereas during baseline ventilation no pause was used. To avoid the effects of different flows and tidal volumes[10,11] and hence inspiratory duration[12] on the measured variables, special care was taken to maintain tidal volume (V=2 ml) and inspiratory flow ($\dot{V}$=10 ml s^{-1}) constant in all animals. Breathing frequency remained constant and equal to 100 bpm during the experiment. Duration of inspiration (TI) was set at 0.2 s and TI/TT was 0.33.

Respiratory mechanics were measured from end-inspiratory occlusions after constant flow inflations (Fig 1).[12–15] After end-inspiratory occlusion, there is an initial fast decrease in tracheal pressure ($\Delta P1$,rs) from the preocclusion value down to an inflection point (Pi,rs). Values of Pi were obtained by back-extrapolation to the time corresponding to Pmax using computer-fitted curves, as described by Jackson, Milhorn and Norman.[16] This was facilitated by taping the records against time expansion as required. A slow pressure decay ($\Delta P2$,rs) ensues until a plateau is reached. This plateau corresponds to the elastic recoil pressure of the respiratory system (Pel,rs). $\Delta P1$,rs selectively reflects the pressure required to overcome the combination of airway, pulmonary and chest wall resistances in normal animals[10,12,15] and humans,[11] and $\Delta P2$,rs reflects the pressure spent on viscoelastic properties or stress relaxation of lung and chest wall tissues, together with a small contribution from *pendelluft* (static readjustment of dynamic regional lung volume differences resulting from time constant inequalities) in normal situations.[11,15] The same procedures apply to chest wall pressure (Pw), giving values for $\Delta P1$,w, Pi,w, $\Delta P2$,w and Pel,w, respectively. Transpulmonary pressures ($\Delta P1$,L, Pi,L, $\Delta P2$,L and Pel,L) were calculated by subtracting chest wall data from the corresponding values pertaining to the respiratory system. Total pressure decrease (ΔPtot) is equal to the sum of $\Delta P1$ and $\Delta P2$ giving values of ΔPtot,rs, ΔPtot,L and ΔPtot,w.

Respiratory system, lung and chest wall static elastances (Est,rs, Est,L and Est,w, respectively) were calculated by dividing Pel,rs, Pel,L and Pel,w, respectively, by VT Dynamic elastances of the respiratory system, lung and chest wall (Edyn,rs, Edyn,L and Edyn,w, respectively) were obtained by dividing Pi,rs, Pi,L and Pi,w, respectively, by VT. ΔE was calculated as the difference Edyn–Est, giving values of ΔE,rs, ΔE,L and ΔE,w. Data relating to respiratory system, lung and chest wall elastances were presented in terms of static elastance and ΔE instead of dynamic elastance as the former represent, respectively, the elastic and visco-

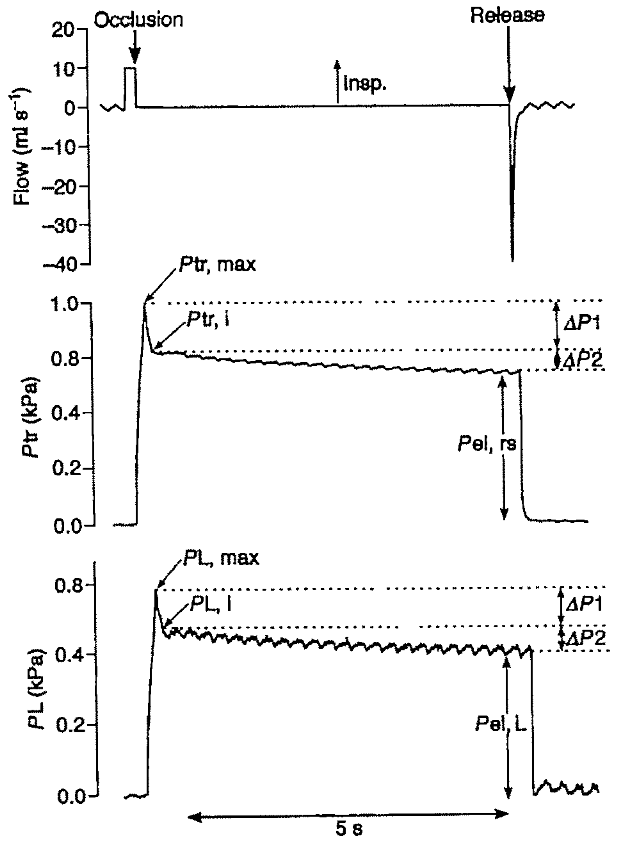


Fig 1 Tracings from a typical experiment showing flow (top), tracheal (*P*tr) (middle) and transpulmonary (*P*L) (bottom) pressures. Airway occlusion at end-inspiration was performed at a point indicated in the top panel After occlusion, there was a sudden decrease in pressures from peak values (*P*max) to initial pressures followed by a gradual decrease until plateau pressures (*P*el) were reached. Occlusion was then released, as indicated in the top panel, and thereafter the animal expired freely (relaxed expiration). Note cardiac oscillation in *P*L. Insp=Inspiration; *P*tr,max=peak tracheal pressure; *P*tr,i=tracheal pressure at inflection point, *P*el,rs=elastic recoil pressure of the respiratory system, *P*L,max=peak transpulmonary pressure, PL,i=transpulmonary pressure at the inflection point; *P*el,L=lung elastic recoil pressure; and Δ*P*1 and Δ*P*2=initial and slow pressure decreases after end-inspiratory occlusion.

elastic properties of the respiratory system.[12] Measurements of respiratory mechanics were performed 6–8 times in each animal in both groups. Immediately before the data sampling period, the airways were aspirated to remove mucus collection and the respiratory system was inflated three times to total lung capacity (TLC) to maintain volume history constant. The experiments lasted ≤30 min.

The delay between the beginning and end of valve closure (10 ms) was compensated for by back-extrapolation of the pressure records to the actual time of occlusion, and the corrections in pressure, although minute, were performed as described previously.[17]

All data were analysed using ANADAT data analysis software (RHT-InfoDat Inc., Montreal, Quebec, Canada).

A continuous record of changes in transcutaneous carbon dioxide level (P_{CO_2}) and arterial blood oxygen saturation (Sa_{O_2}) was performed using a SensorMedics FasTrac (Yorba Linda, CA, USA), and values were 4.9–5.6 kPa and 95–98%, respectively.

Immediately after measurement of respiratory mechanics with the animal still alive, the trachea was clamped at end-expiration and the abdominal aorta and vena cava were sectioned, yielding a massive haemorrhage that quickly killed the animal. Functional residual capacity (FRC) was determined in the following way: the lungs were removed rapidly (on average, in 90 s) and submerged in warm (37°C) 0.9% NaCl solution (saline), the volume displaced was noted and the lungs were weighed. FRC corresponds to the difference between the saline displaced (ml) and lung weight (g), assuming that tissues and saline have identical densities and are equal to 1.0.[18]

After measurement of FRC, the lungs were snap-frozen by immersion in liquid nitrogen to perform a morphometric study.[19] Tissues were fixed in Carnoy's solution (ethanol: cloroform:acetic acid, 70:20:10 by volume) at −70°C for 24 h. Progressively increasing concentrations of ethanol at −20°C were then substituted for Carnoy's solution until 100% ethanol was reached. Tissues were maintained at −20°C for 4 h, warmed to 4°C for 12 h and then allowed to reach and remain at room temperature for 2 h. After fixation, tissue blocks obtained from mid-sagittal slices of the lungs at the level of the axial bronchus were embedded in parafin. Blocks were cut 4-μm thick using a microtome. Coded slides were stained with haematoxylin–eosin.

Microscopic examination was performed by two investigators who were unaware of the origin of the material during scoring. Morphometric analysis was performed with an integrating eyepiece with a coherent system made of a 100-point grid consisting of 50 lines of known length coupled to a conventional light microscope. The volume fraction of collapsed and normal pulmonary areas, and the fraction of lung occupied by large-volume, gas-exchanging air spaces (hyperinflation—structures with a morphology distinct from that of alveoli and wider than 120 μm) were determined using the point-counting technique,[19] at a magnification of ×40 across 10 random, non-coincident microscopic fields. The internal diameters of the central and peripheral airways were computed by counting the points falling on the airway lumen and the points falling on airway smooth muscle and on the epithelium. The perimeters of the airways were estimated by counting the intercepts of the lines of the integrating eyepiece with the epithelial basal membrane. This procedure was repeated four times for each airway. The areas of smooth muscle and airway epithelium were corrected in terms of airway perimeter by dividing their values by the number of intercepts of the line system with the epithelial basal membrane of the corresponding airway. Because the number of intercepts (NI) of the lines with the epithelial basal membrane is proportional to the airway perimeter, and the number of points (NP) falling on airway lumen is proportional to airway area, the magnitude of bronchoconstriction

Table 1 Respiratory data in rats anaesthetized with pentobarbital (control group) and halothane (halothane group). Values are mean (SD) [range] of eight animals (8–10 determinations/rat). rs=Respiratory system; L=lung, w=chest wall; ΔPtot, $\Delta P1$ and $\Delta P2$=total, initial and slow pressure decreases after end-inspiratory occlusion, respectively, Est=static elastance, ΔE=difference between dynamic and static elastances. ns=No significant difference between control and halothane groups

	Control group	Halothane group	*P*
Flow (ml s^{-1})	10.22 (0.31) [10.1–11.0]	9.87 (0.20) [9.4–10.1]	ns
Tidal volume (ml)	2.02 (0.03) [1.97–2.09]	1.97 (0.11) [1.73–2.13]	ns
FRC (ml)	2.22 (0.19) [2.05–2.31]	2.19 (0.09) [1.96–2.46]	ns
Respiratory system			
ΔPtot,rs (kPa)	0.34 (0.07) [0.27–0.50]	0.39 (0.05) [0.29–0.47]	ns
$\Delta P1$,rs (kPa)	0.17 (0.04) [0.14–0.20]	0.13 (0.01) [0.11–0.15]	0.007
$\Delta P2$,rs (kPa)	0.17 (0.04) [0.13–0.25]	0.26 (0.05) [0.17–0.32]	0.002
Lung			
ΔPtot,L (kPa)	0.24 (0.08) [0.16–0.32]	0.29 (0.05) [0.22–0.36]	ns
$\Delta P1$,L (kPa)	0.14 (0.03) [0.10–0.18]	0.10 (0.02) [0.06–0.12]	0.028
$\Delta P2$,L (kPa)	0.10 (0.04) [0.04–0.14]	0.19 (0.04) [0.14–0.25]	0.003
Chest wall			
ΔPtot,w (kPa)	0.10 (0.02) [0.04–0.12]	0.10 (0.03) [0.06–0.12]	ns
$\Delta P1$,w (kPa)	0.04 (0.01) [0.02–0.06]	0.03 (0.01) [0.02–0.05]	ns
$\Delta P2$,w (kPa)	0.06 (0.02) [0.02–0.08]	0.07 (0.02) [0.04–0.08]	ns
Elastance			
Est,rs (kPa ml^{-1})	0.33 (0.03) [0.29–0.39]	0.45 (0.06) [0.33–0.52]	0.0001
Est,L (kPa.ml^{-1})	0.26 (0.04) [0.22–0.33]	0.38 (0.06) [0.29–0.44]	0.0002
Est,w (kPa ml^{-1})	0.07 (0.01) [0.05–0.09]	0.07 (0.02) [0.05–0.10]	ns
Difference between dynamic and static elastances			
ΔE,rs (kPa ml^{-1})	0.08 (0.02) [0.06–0.11]	0.13 (0.02) [0.10–0.16]	0.0005
ΔE,L (kPa ml^{-1})	0.05 (0.02) [0.02–0.07]	0.10 (0.02) [0.08–0.12]	0.001
ΔE,w (kPa ml^{-1})	0.03 (0.01) [0.01–0.04]	0.35 (0.01) [0.02–0.05]	ns

(contraction index (CI)) was computed by the relationship: $CI = NI \div \sqrt{NP}$.[20]

To confirm that the dose of pentobarbital did not constrict or relax the airways, another group of five animals (290–310 g) were killed by cervical dislocation (group CD), their lungs removed and prepared for lung histology as described previously.

Statistical analysis was performed using the Student's *t* test. To compare morphometric variables in each group, we first tested if the data were distributed normally (Komolgorov–Smirnov test with Lilliefor's correction) and the homogeneity of variances (Levene median test). In all cases both conditions were satisfied, and one-way analysis of variance (ANOVA) was used. If multiple comparisons were required, the Student–Newman–Keuls test was applied. Significance was set at 5%.

Results

There were no significant differences between groups for mean constant inspiratory flow or volume (Table 1). There was no significant difference in FRC between the control and halothane groups.

Table 1 shows respiratory system, lung and chest wall ΔP values, static elastances and ΔE values obtained in control and halothane animals. ΔPtot,w, $\Delta P1$,w, $\Delta P2$,w, Est,w and ΔE,w were identical in both groups. In rats anaesthetized with halothane, $\Delta P1$,rs was 35% less than in those anaesthetized with pentobarbital because of a smaller $\Delta P1$,L (37%). In addition, $\Delta P2$,rs was greater (57%) in the halothane than in control group because of an increase in $\Delta P2$,L (86%). Consequently, there were no significant differences between groups for ΔPtot,rs or ΔPtot,L. Halothane anaesthesia produced Est,rs, Est,L, ΔE,rs and ΔE,L values that were greater than those in the control group (+39%, +50%, +59% and +87%, respectively).

Table 2 Morphometric data in rats anaesthetized with pentobarbital (control group), halothane (halothane group) or after cervical dislocation (CD group). Values are mean (SD) of eight rats or five rats after cervical dislocation. All values are percentage of normal, collapsed and hyperinflated areas in 10 random, non-coincident fields per rat. *Significantly different from control ($P<0.05$)

	Control group	Halothane group	CD group
Normal	87.5 (8.14)	70.5 (5.15)*	84.6 (5.73)
Alveolar collapse	4.06 (1.74)	13.4 (2.92)*	3.84 (1.80)
Alveolar hyperinflation	2.43 (0.93)	6.06 (1.40)*	2.53 (0.67)
Contraction index	0.11 (0.01)	0.07 (0.01)*	0.11 (0.02)

Mean percentages of normal, collapsed and hyperinflated areas in the control, halothane and CD groups are shown in Table 2. Halothane produced a greater degree of collapse and hyperinflation compared with the control and CD groups. An increased internal diameter of the central airways was also detected in the halothane compared with the control and CD groups. There was no difference between the control and CD groups.

Discussion

Our main finding in rats with no pre-existing airway tone was that halothane anaesthesia decreased pulmonary resistive pressure dissipation (i.e. airway resistance) and increased viscoelastic/inhomogeneous and elastic pressures applied to the lung (reflecting stiffening of lung tissues). The former findings were supported by the histological demonstration of airway dilatation and the latter were related to increased areas of collapse and hyperinflation. Under the conditions studied, total pulmonary pressure dissipation (i.e. pulmonary resistance) during halothane administration remained unchanged, in agreement with previous results.[5 6] Consequently, these opposite effects resulted in no apparent change in mechanical properties when 'total' behaviour was considered. However, there were reciprocal changes in 'total' mechanics during halothane anaesthesia in normal animals and subjects.

Halothane inhibits increased pulmonary resistance produced by stimuli such as Ascaris antigen, histamine, methacholine and vagus nerve stimulation.[1–4] Vettermann and colleagues applied alveolar capsules to the pleural surfaces of dogs during halothane anaesthesia and observed that airway and tissue resistances decreased whereas pulmonary elastance remained unaltered.[3] The same resistive changes were described using P–V curves.[3]

Gallamine, an antagonist of muscarinic M2-type receptors, was used to produce neuromuscular block and many studies have shown that although it has anticholinergic properties, airway resistance is unchanged.[21 22] Barbiturates can inhibit vagal reflexes[23] and directly contract or relax airway smooth muscle, depending on the dose[24] and species studied. To verify the effects of pentobarbital and gallamine in our preparation, another group of rats was killed by cervical dislocation (CD) and their lungs analysed histologically. The same histological pattern was observed in the control and CD groups, suggesting that pentobarbital and gallamine did not significantly alter lung morphometry compared with CD animals. Consequently, the mechanical properties of both groups were probably similar.

As shown in Table 1, halothane anaesthesia produced smaller pulmonary resistive pressure dissipation. As reported previously, pulmonary resistive pressure is directly related to airway resistance.[25] It follows that in our study, halothane produced a decrease in airway resistance. Halothane anaesthesia increased the internal diameter of the central airways (+57%), supporting our mechanical findings. This finding is consistent with previous measurements of lung resistance in stimulated airways,[1–4] and could be explained by a neural reflex pathway and/or a direct action on the smooth muscle cell and its receptor systems.[26] In addition, direct actions of halothane on airway smooth muscle can only be significant if sufficient neural traffic reaches the smooth muscle cell.[26] Therefore, the relative importance of neurally mediated and direct effects of halothane in antagonizing bronchoconstriction are dependent strongly on the applied stimulus and on the preparation (intact *vs* isolated lungs).

In our study, $\Delta P2$,L increased significantly (Table 1) during halothane anaesthesia. Lung histology showed an increase in the percentage values for alveolar hyperinflation and collapse in the halothane group. From a total of 800 fields in the halothane group, only 2% demonstrated hyperinflation associated with alveolar collapse. Thus it seems that relaxation of the airways and atelectasis (the latter possibly caused by changes in surfactant properties[27]) produced by halothane anaesthesia, could be sufficient to affect regulation of the distribution of ventilation. Under these conditions *pendelluft* and mechanical inhomogeneities could be made worse, increasing $\Delta P2$,L. In two previous studies, tissue resistance decreased during halothane anaesthesia.[3 4] In the first study,[3] the analysis was performed in isolated lungs that had been previously degassed and inflated to an airway pressure of 2.5 kPa, and in the second,[4] the vagus nerve was stimulated in an open-chest approach. Hence these experiments are not comparable.

As shown in Table 1, the overall pressure (ΔPtot,L) used to overcome resistive and viscoelastic (central and peripheral mechanical components) elements was not modified by halothane, and is consistent with previous measurements of pulmonary resistance.[5 6] This finding derives from a statistically significant decrease in $\Delta P1$,L, together with an increase in $\Delta P2$,L. In contrast, in previously constricted airways, a decrease in pulmonary resistance was reported after halothane administration.[1–4] As chest wall pressures were not altered by halothane (Table 1), respiratory mechanics reflect the pulmonary component.

Halothane produced a higher Est,L which caused an increase in Est,rs (Table 1), indicating that the pulmonary and respiratory system elastic components of respiratory impedance were augmented under the present experimental conditions, as reported previously.[6] The increase in Est,L could be attributed to atelectasis (Table 2). However, a change in surfactant properties cannot be excluded.[27]

ΔE,rs and ΔE,L increased significantly during halothane anaesthesia whereas ΔE,w remained unaltered (Table 1), suggesting that lung (and thus respiratory system) viscoelasticity/inhomogeneity became more prominent after halothane anaesthesia. This finding was confirmed by the increase in $\Delta P2$,L (Table 1), as discussed above. During halothane anaesthesia, Edyn,L is elevated.[4] We demonstrated that both its static (Est,L) and viscoelastic (ΔE,L) components contributed to the increase in Edyn,L. A decrease in Edyn,L has also been reported, but these experiments were performed in previously constricted lungs[26] or in isolated lobes.[3]

The effect of halothane on airway resistance depends on the interaction between the effects of a reduction in lung volume and anaesthetic-induced relaxation of airway smooth muscle.[28] This could explain why halothane does not apparently affect pulmonary resistance. In our experiments, volume, flow and breathing frequency were similar in both groups, and there was no significant difference in FRC between the control and halothane groups. Hence the mechanical changes were solely a result of halothane anaesthesia.

In summary, we found that halothane anaesthesia in rats without pre-existing airway tone (1) increased viscoelastic/inhomogeneous and elastic pressures applied to the lung, reflecting stiffening of lung tissues and (2) decreased pulmonary resistive pressure dissipation (i.e. airway resistance).

Acknowledgements

Supported by the Program of the Centers of Excellence (PRONEX-MCT), Brazilian Council for Scientific and Technological Development (CNPq), Financing for Studies and Projects (FINEP), and Graduate Teaching and Research Council of the Federal University of Rio de Janeiro (CEPG-UFRJ) We thank Mr Antonio Carlos de Souza Quaresma for technical assistance

References

1 Hirshman CA, Bergman NA. Halothane and enflurane protect against bronchospasm in an asthma dog model. *Anesth Analg* 1978; **57**: 629–33

2 Hickey RF, Graf PD, Nadel JA, Larson CP. The effects of halothane and cyclopropane on total pulmonary resistance in the dog. *Anesthesiology* 1969; **31**: 334–43

3 Vettermann J, Warner DO, Brichant JF, Rehder K. Halothane decreases both tissue and airway resistances in excised canine lungs. *J Appl Physiol* 1989; **66**: 2698–703

4 Warner DO, Vettermann J, Brusasco V, Rehder K. Pulmonary resistance during halothane anesthesia is not determined only by airway caliber. *Anesthesiology* 1989; **70**: 453–60

5 Colgan FJ. Performance of lungs and bronchi during inhalation anesthesia. *Anesthesiology* 1965; **26**: 779–85

6 Behrakis PK, Higgs BD, Baydur A, Zin WA, Milic-Emili J. Respiratory mechanics during halothane anesthesia and anesthesia–paralysis in humans. *J Appl Physiol* 1983; **55**: 1085–92

7 Mortola JP, Novoraj A Two-sidearm tracheal cannula for respiratory airflow measurements in small animals. *J Appl Physiol* 1983; **55**: 250–3

8 Chang HK, Mortola JP. Fluid dynamic factors in tracheal pressure measurements *J Appl Physiol* 1981; **51**: 218–25

9 Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the oesophageal balloon technique. *Am Rev Respir Dis* 1982; **126**: 788–91

10 Kochi T, Okubo S, Zin WA, Milic-Emili J. Chest wall and respiratory system mechanics in cats: effects of flow and volume. *J Appl Physiol* 1988; **64**. 2636–46

11 D'Angelo E, Calderini E, Torri G, Robbato FM, Bono D, Milic-Emili J. Respiratory mechanics in anesthetized paralyzed humans: effects of flow, volume, and time *J Appl Physiol* 1989; **67**: 2556–64

12 Similowski T, Levy P, Corbeil C, *et al.* Viscoelastic behavior of lung and chest wall in dogs determined by flow interruption. *J Appl Physiol* 1989; **67**: 2219–29

13 Bates JHT, Rossi A, Milic-Emili J. Analysis of the behavior of the respiratory system with constant inspiratory flow. *J Appl Physiol* 1985; **58**: 1840–8

14 Bates JHT, Baconnier P, Milic-Emili J A theoretical analysis of the interrupter technique for measuring respiratory mechanics. *J Appl Physiol* 1988; **64**: 2204–14

15 Kochi T, Okubo S, Zin WA, Milic-Emili J. Flow and volume dependence of pulmonary mechanics in anesthetized cats *J Appl Physiol* 1988; **64**: 441–50

16 Jackson AC, Milhorn HT, Norman JR. A reevaluation of the interrupter technique for airway resistance measurement. *J Appl Physiol* 1974; **36**: 264–8

17 Bates JHT, Hunter IW, Sly PD, Okubo S, Filiatrault S, Milic-Emili J. Effect of valve closure time on the determination of respiratory resistance by flow interruption. *Med Biol Eng Comput* 1987; **25**: 136–40

18 Agostoni E, Thimm FF, Fenn WO. Comparative features of the mechanics of breathing *J Appl Physiol* 1959; **14**· 679–83

19 Weibel ER. Morphometry: stereological theory and practical methods. In: Gil J, ed. *Models of Lung Disease—Microscopy and Structural Methods.* New York: Marcel Dekker, 1990; 199–247

20 Sakae RS, Leme AS, Dolhnikoff M, *et al.* Neonatal capsaicin treatment decreases airway and pulmonary tissue responsiveness to methacholine. *Am J Physiol* 1994; **266**: L23–9

21 Leff A. Endogenous regulation of bronchomotor tone *Am Rev Respir Dis* 1989; **137**· 1198–216

22 Lehane JR. Assesment of pulmonary airway calibre. *Br J Anaesth* 1992; **54**. 751–61

23 Bernstine ML, Berker E, Cullen M. The bronchomotor effects of certain intravenous barbiturates on vagal stimulation in dogs. *Anesthesiology* 1957; **18**: 866–70

24 Lenox WC, Mitzner W, Hirshman CA. Mechanism of thiopental-induced contriction of guinea pig trachea. *Anesthesiology* 1990; **72**: 921–5

25 Saldiva PHN, Zin WA, Santos RLB, Eidelman DH, Milic-Emili J Alveolar pressure measurement in open-chest rats. *J Appl Physiol* 1992; **72**: 302–6

26 Warner DO, Vettermann J, Brichant JF, Rehder K. Direct and neurally mediated effects of halothane on pulmonary resistance in vivo. *Anesthesiology* 1990; **72**: 1057–63

27 Molliex S, Crestani B, Dureuil B, *et al.* Effects of halothane on surfactant biosynthesis by rat alveolar type II cells in primary culture. *Anesthesiology* 1994; **81**: 668–76

28 Joyner MJ, Warner DO, Rehder K Halothane changes the relationships between lung resistances and lung volume. *Anesthesiology* 1992; **76**: 229–35

British Journal of Anaesthesia 84 (3): 378–93 (2000)

BJA

REVIEW ARTICLE

Central nervous system complications of cardiac surgery†

J. E. Arrowsmith[1]*, H. P. Grocott[2], J. G. Reves[2] and M. F. Newman[2]

[1]*Department of Anaesthesia, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE, UK.*
[2]*Division of Cardiothoracic Anesthesia, Department of Anesthesiology, Box 3094,*
Duke University Medical Center, Durham, NC 27710, USA
**Corresponding author*

Br J Anaesth 2000; **84**: 378–93

Keywords: surgery, cardiovascular; surgery, postoperative period; heart, cardiopulmonary bypass; brain, function; psychological responses, postoperative; complications, neurological; complications, stroke

While the number of patients undergoing surgery for valvular and other types of heart disease has remained fairly constant, the number undergoing coronary revascularization procedures is increasing (Fig. 1). Because of many technological advances over the past four decades, there has been a steady decrease in the mortality and morbidity associated with these procedures. Nevertheless, neurological injury remains an important cause of postoperative morbidity[91] and is responsible for an increasing proportion of perioperative deaths.[44 158] Since the introduction of cardiopulmonary bypass (CPB) in the early 1950s, the neurological sequelae of cardiac surgery have been a major concern. Identification of risk factors for adverse neurological and neuropsychological outcomes has led to the development of physical and pharmacological neuroprotective strategies targeted at the 'at risk' population.[111 123]

Neurological injury after cardiac surgery

Advances in medical care and the introduction of broader indications for surgery has meant that patients previously deemed inoperable are now considered suitable candidates for surgery. Over the past 20 yr, there has been a steady increase in the average age of patients undergoing cardiac surgery.[123] This increase has been accompanied by a rise in both the severity of cardiac disease at the time of surgery and the reoperation rate for recurrent disease.[67] Nevertheless, the likelihood of dying or sustaining a major complication after cardiac surgery in the late 1990s is significantly lower than that in the 1950s. Not unreasonably, most patients expect to survive cardiac surgery intact, make a good functional recovery and live longer. A significant number of patients however suffer a perioperative complication involving the central nervous system (CNS).

Adverse neurological outcome from cardiac surgery is the result of damage to the brain, spinal cord and/or peripheral nerves. CNS injury ranges in severity from subtle changes in personality, behaviour and cognitive function to fatal brain injury—the 'cerebral catastrophe' (Table 1). A major neurological complication after otherwise successful surgery represents a devastating outcome for patient and their family. The social and economic impact is enormous.

Measures of neurological outcome after cardiac surgery

A wide variety of techniques have been used to assess adverse neurological events after cardiac surgery (Table 2) with the incidence of stroke and cognitive dysfunction being the most frequently used outcome measures. Early retrospective studies in this area could only detect what they set out to look for—neurological (e.g. coma, hemiparesis, seizures, blindness) and psychological (e.g. depression, disorientation and confusion)—problems that were sufficiently obvious to be noticed *and* documented.

The introduction of psychometric testing, typically measures of memory, attention, visuospatial ability and motor speed, broadened the scope and power of investigations.[17] Prospective studies not only demonstrated the value of a multimodal (i.e. neurological and neuropsychological) approach, but highlighted the need for investigators to have the appropriate training and background.[135]

Several difficulties associated with perioperative neurocognitive testing continue to challenge the research community. There is as yet no 'gold standard' against which to compare new tests. In addition, there is neither agreement

---

†This article is accompanied by Editorial II.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

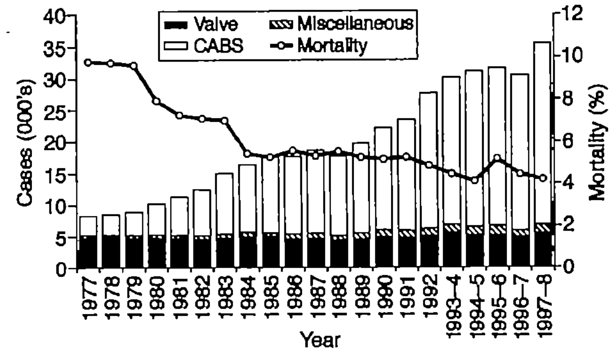


Fig 1 The UK Society of Cardiothoracic Surgeons (SCTS) register 1977–1998. Summary of procedures carried out for ischaemic, valvular and miscellaneous acquired heart disease, and overall operative mortality. Adapted from data obtained from the SCTS web site (http://www.scts.org/doc/2104) and reproduced with permission

Table 1 Types and initial incidence of neurological complications after cardiac surgery (reproduced and modified with permission from Shaw and colleagues[135])

Complication	Incidence
Fatal brain injury	0.3%
Non-fatal diffuse encephalopathy	
Depressed conscious level	3%
Behavioural changes	1%
Intellectual/cognitive dysfunction	30–79%
Seizures	
Choreoathetosis	0.3%
Ophthalmological	
Visual field defects	25%
Reduced visual acuity	4.5%
Focal brain injury (stroke)	2–5%
Primitive reflexes	39%
Spinal cord injury	0–0.1%
Peripheral nerve injury	
Brachial plexopathy	7%
Other peripheral neuropathy	6%

on which tests or groups of tests should be used, nor what is (are) the optimal time(s) for administration.[151] There is broad agreement that using a large number of tests is preferable to using only a few. The incidence of cognitive decline is reported to be higher in studies in which a larger number of tests were used than in those where only a few tests were used. Using a larger number of tests however, increases both administration time and the likelihood that some patients will not be able to complete all tests. The number of tests used and their timing in relation to surgery affects measured outcome.[17]

There is no universally accepted method of analysing neurocognitive test results and therefore no standard for defining the incidence and severity of cognitive decline based on changes in test performance.[16] By focusing solely on a decline in cognitive function, most investigators have ignored the fact that, with repeated testing, normal volunteers tend to show improvement in performance, a phenomenon known as the practice effect.[113] Cognitive impairment should perhaps more correctly be defined as decline and failure to improve.[49 84] Furthermore, if an age-matched control group is not used in late follow-up studies, it may be impossible to distinguish persistent perioperative neurological problems from the effects of normal ageing processes, depression or dementia.[40]

Many confounding factors make it difficult to attempt direct comparisons between studies that have used different methodologies.[78] In an effort to address these problems, a consensus on the use of these tests is beginning to emerge.[97 98]

Markers of neuronal injury

In addition to neurocognitive testing, proteins released by the injured brain have been used to measure brain injury. After cerebral hypoxia–ischaemia, numerous substances have been shown to be released from neurones, glia, endothelium, platelets and leucocytes (Table 3). Quantification of these substances offers the potential for rapid diagnosis, making possible early interventions aimed at reducing cerebral injury. Furthermore, if the degree of elaboration of a biochemical marker can be shown to correlate with clinical (neurological and cognitive) outcome, large interventional studies could be designed that do not rely on costly and time consuming neurological and neuropsychological testing.

Although a marker of neuronal injury may provide an indication of the severity of a cerebral injury, it cannot provide information on the anatomical distribution and clinical impact of that injury. A small infarct in the internal capsule may be associated with modest release of a marker substance yet produce a disabling hemiplegia, whereas a considerably larger infarct in a frontal lobe, accompanied by massive release of marker, may produce few symptoms or physical signs.

Brain-specific creatine phosphokinase (CPK-BB) was one of the first markers to be evaluated.[156] Marked increases in cerebrospinal fluid (CSF) concentrations were detected in dogs subjected to 60 min of CPB. Incorporation of a 40-µm arterial line filter resulted in significantly lower CSF CPK-BB concentrations compared with those in unfiltered animals. In a clinical study conducted at the Cleveland Clinic, 413 of 421 (98%) patients undergoing coronary artery bypass surgery (CABS) had increased blood concentrations of CPK-BB after surgery. There was, however, no correlation between CPK-BB concentration and the occurrence of encephalopathy or stroke.[21]

The use of CSF adenylate kinase (CSF-AK) as a marker of cerebral injury after cardiac surgery was reported by Åberg and colleagues.[2] A subsequent publication reported a significant correlation between CSF-AK and performance in psychometric tests.[1] Further work characterizing CSF markers has been limited because of the methodological problems of lumbar puncture in patients who have been heparinized for CPB.

The marker that has received the most interest recently is astroglial protein S100β. The numerous functions of

Table 2 Investigational methods used in the study of adverse neurological outcome after cardiac surgery

Pathological	Gross and microscopic postmortem examination
Clinical	Retrospective chart review for mortality and gross neurological, psychiatric, cognitive complications
	Prospective neurological and psychiatric examination
	Neuropsychological/cognitive function testing, anxiety and depression inventories
	Subjective (patient±spouse) reports of cognitive function
Financial	Duration of intensive care
	Length of hospital stay
	Patient charges
Social	Activities of daily living
	Return to work
	Resumption of sexual activity
Ultrasound	Transoesophageal echocardiography±epiaortic ultrasound assessment of aortic atheromatous disease
	Carotid and transcranial Doppler quantification of microemboli
Brain imaging	Brain computed tomography (CT)
	Magnetic resonance imaging and spectroscopy (MRS)
	Positron emission tomography (PET)
Electrophysiological	Electroencephalography (EEG)
	Processed EEG (cerebral function analysing monitor—CFAM), somatosensory evoked potentials (SSEP)
Biochemical	Blood and cerebrospinal fluid markers of cerebral injury
	Blood glucose, arterial pH and blood gases
Others	Cerebral near infra-red spectroscopy (NIRS)
	Jugular bulb oxygen saturation
	Retinal fluorescein angiography
	Regional cerebral blood flow (rCBF)

Table 3 Potential biochemical markers of brain injury

Source	**Marker(s)**
Glia	S100b, myelin basic protein (MBP)
	Glial fibrillary acidic protein (GFAP)
Neurones	Neurone specific enolase (NSE), adenylate kinase (AK)
	Creatine phosphokinase brain isoform (CPK-BB)
	Guanine nucleotide binding protein G0, calbidin-D
	Lactate dehydrogenase (LDH), glutamate
Inflammatory cells	Interleukin-6, transforming growth factor-β
	Adhesion molecules (ICAM-1, E-selectin, neural cell adhesion molecule–NCAM)
Metabolic	Lactate, Cu-Zn superoxide dismutase (CuZn-SOD)

S100β include promotion of axonal growth, glial proliferation, neuronal differentiation and calcium homeostasis.[73] Increased concentrations of S100β in both blood and CSF have been found after acute stroke, transient ischaemic attacks, head injury, intracranial haemorrhage and post-cardiac arrest coma, in addition to Alzheimer's disease and Down's syndrome.[73] In acute stroke, the degree of S100β elevation correlates well with infarct volume and neurological outcome.[73]

Several studies have demonstrated an increase in S100β after cardiac surgery. Westaby and colleagues reported a relationship between S100β concentrations and age, aortic cross-clamp time and CPB duration.[166] Patients with carotid artery stenosis had higher concentrations of S100β than those who did not and patients who had CABS without CPB showed no increase in S100β. Peak postoperative concentrations of S100β have been shown to correlate with intraoperative cerebral microemboli quantified with transcranial Doppler sonography.[50] The Oxford group has shown that, compared with controls, the use of an arterial line filter decreased the number of patients who had abnormal increases in S100β after surgery.[153] The same group has also shown that intracardiac surgery (e.g. mitral or aortic valve procedures) is associated with a greater postoperative increase in S100β than CABS.[154]

Risk factors for adverse neurological outcome

Soon after the introduction of CPB into clinical practice, reports of neurological injury after cardiac surgery began to appear in the literature. Early reports were small and retrospective, focusing on clinical manifestations in survivors and neuropathological findings in non-survivors. The late 1960s and early 1970s heralded the publication of several large, retrospective studies and the recognition of the importance of patient age, cerebral hypoperfusion and cerebral embolism. During the next decade, the focus of prospective investigation moved away from stroke and coma (which were becoming increasingly uncommon) to more subtle psychological, cognitive and behavioural outcomes. More recently, investigators have examined the causes and mechanisms of neurological injury, developed indices of risk by defining predictive perioperative risk factors, and tested the beneficial effects of physical and pharmacological interventions.

Arguably one of the most significant contributions in recent years is the prospective, observational study conducted by the Multicenter Study of Perioperative Ischemia (McSPI) group at 24 US medical institutions between 1992 and 1994. The study sought to determine the incidence of neurological injury after CABS, identify independent predictors of these adverse outcomes and assess their impact on resource utilization. Two categories of adverse neurological outcome were defined: type I—non-fatal stroke, transient ischaemic attack (TIA), stupor or coma at the time of discharge, or death caused by stroke or hypoxic encephalopathy; and type II—new deterioration in intellectual function, confusion, agitation, disorientation, memory

Table 4 Adjusted odds ratios [95% confidence intervals] for type I and type II cerebral outcomes associated with selected risk factors from the McSPI and IREF study. IABP=intra-aortic balloon pump; AP=arterial pressure, CABS=coronary artery bypass surgery (reproduced with permission from Roach and colleagues[123])

Risk factor	Type I outcomes	Type II outcomes
Proximal aortic atherosclerosis	4.52 [2.52–8.09]	
History of neurological disease	3.19 [1.65–6.15]	
Use of IABP	2.60 [1.21–5.58]	
Diabetes mellitus	2.59 [1.46–4.60]	
History of hypertension	2.31 [1.20–4.47]	
History of pulmonary disease	2.09 [1.14–3.85]	2.37 [1.34–4.18]
History of unstable angina	1.83 [1.03–3.27]	
Age (per additional decade)	1.75 [1.27–2.43]	2.20 [1.60–3.02]
Admission systolic AP >180 mm Hg		3.47 [1.41–8.55]
History of excessive alcohol intake		2.64 [1.27–5.47]
History of CABS		2.18 [1.14–4.17]
Arrhythmia on day of surgery		1.97 [1.12–3.46]
Antihypertensive therapy		1.78 [1.02–3.10]

deficit or seizure without evidence of focal injury. More than 30% of patients were 70 yr or older and there was a high prevalence of hypertension, unstable angina, cardiac failure and diabetes mellitus. In all, 129 of 2108 (6.1%) patients had an adverse neurological outcome in the perioperative period. Type I outcomes occurred in 66 of 2108 (3.1%) patients and included eight deaths as a result of cerebral injury, 55 non-fatal strokes, two TIA and one case of stupor at the time of discharge. Type II outcomes occurred in 63 of 2108 (3.0%) patients and included 55 patients with intellectual dysfunction and eight with seizures. The wide variation in institutional outcome rates for both type I (1–13.8%) and type II (0–9.3%) outcomes is cause for concern and has yet to be fully addressed.

Stepwise logistic regression analysis identified eight significant, independent predictors of type I outcomes and seven significant, independent predictors of type II outcomes (Table 4). Although similar, the predictors for the two outcome types were not identical.

Factors found not to be significant predictors were: perioperative hypotension (systolic arterial pressure <40 mm Hg during CPB or <80 mm Hg at other times for more than 10 min), intraoperative use of an apical vent to decompress the left ventricle, congestive cardiac failure on the day of surgery and a history of peripheral vascular disease. Adverse neurological outcome was associated with higher in hospital mortality, increased duration of intensive care and postoperative hospital stay, increased patient charges and increased likelihood of being discharged to an intermediate or long-term care facility.

Using data obtained from the McSPI study, the Duke group went on to develop a model to predict the development of stroke after CABS.[111] Using preoperative patient factors, the so-called *stroke index* allows rapid assessment of risk (Fig. 2).

More recently, the McSPI group have reported adverse neurological outcomes in 43 of 273 (16%) patients undergoing combined intracardiac and coronary artery procedures.[168] The authors concluded that this surgical population was at *extraordinary* risk of adverse cerebral outcome.

Risk factor	Score
Age	(Age –25) x 1.43
Unstable angina	14
Diabetes mellitus	17
Neurological disease	18
Prior CABS	15
Vascular disease	18
Pulmonary disease	15

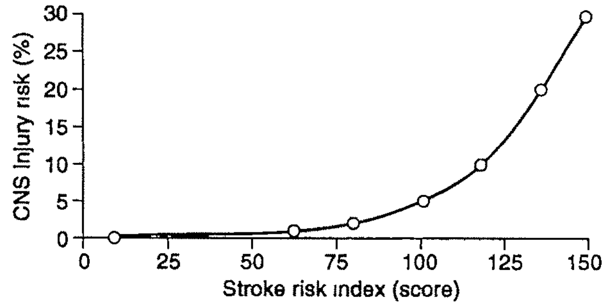


Fig 2 Multicentre preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Definitions: diabetes mellitus—history of either type I or type II diabetes or insulin use on admission or before operation; neurological disease—previous stroke or transient ischaemic attack; vascular disease—peripheral vascular disease, known carotid vascular disease, claudication or vascular surgery; pulmonary disease—emphysema, chronic bronchitis, asthma, restrictive lung disease. CABS=coronary artery bypass surgery, CNS=central nervous system. Adapted with permission from Newman and colleagues [111]

Patient age

Of all the factors thought to be predictive of neurological and neuropsychological injury in cardiac surgery, age is probably the most robust[32 43 108 123 158] (Fig. 3). Although the elderly appear to retain cerebral autoregulation, they are at increased risk of stroke, particularly in the presence of severe aortic atherosclerosis and occult cerebrovascular disease.[15 105] The elderly are more likely to have reduced baseline cognitive function so that a relatively small perioperative decline may have a significant impact on independent living.

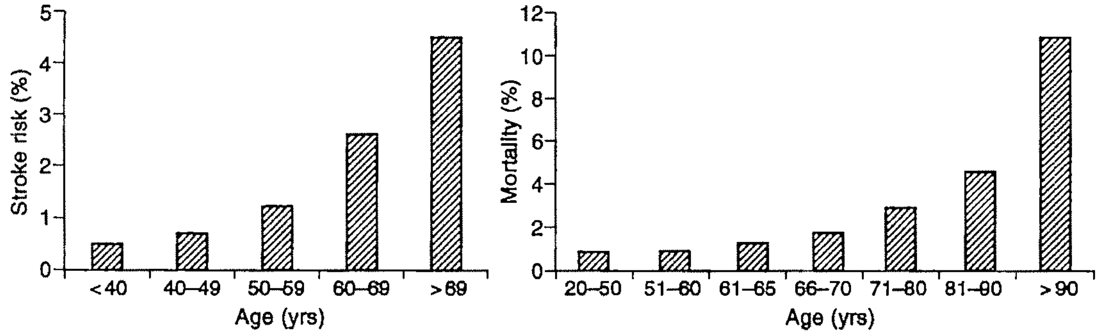


Fig 3 Effect of age on the risk of stroke (left) and mortality (right) after coronary artery bypass surgery. Reproduced with permission from Cosgrove and colleagues[32] and the US Society of Thoracic Surgeons (http://www.sts.org/graphics/sts/db/us98/gchart63.gif), respectively

Sex

Few studies have specifically examined the influence of sex on neurological outcome after cardiac surgery.[43] The main reason for this is that men greatly outnumber women in the adult cardiac surgical population. Data from the US Society of Thoracic Surgeons (http://www.sts.org/outcomes) for the years 1995 to 1996 suggest that operative mortality was significantly greater in females after both repeat and/or emergency CABS (4.30% *vs* 2.63%; $P<0.0001$) and primary elective CABS (2.9% *vs* 1.5%; $P<0.0001$). A recent report from the Bypass Angioplasty Revascularization Investigation (BARI) group however, suggests that the higher mortality observed in women is a product of higher risk profiles rather than increased gender susceptibility.[65] When risk factors are controlled for, female sex was an independent predictor of *improved* 5-yr survival.

Laboratory evidence suggests that oestrogens have a vital role in neuronal growth, differentiation and survival.[141] Furthermore, oestrogens also appear to play an important and specific role in cognitive function in women.[136] The finding that oestrogen administration reverses memory deficits in women rendered hypo-oestrogenic with leuprolide acetate (a gonadotrophin releasing hormone agonist) suggests that a study of oestrogen replacement in postmenopausal women undergoing cardiac surgery is warranted.[137]

Severity of cardiac disease and cardiac function

An early study by Blachly and Kloster suggested that low postoperative cardiac output was related to the occurrence and severity of a postoperative brain syndrome or hallucinosis.[12] Lee and colleagues reported that patients who had symptoms of cardiac disease for more than 6 months were more likely to develop neurological damage after coronary artery surgery.[74] Poor preoperative left ventricular function and/or episodes of left ventricular failure have been reported to be associated with worse neurological outcome.[131] [134] Interestingly, the McSPI study found that neither congestive cardiac failure nor arrhythmia on the day of surgery were associated with adverse neurological outcome.[123] It is possible that improvements in critical care, anti-arrhythmic therapy and support of the failing heart have reduced the impact of poor cardiac function on neurological outcome.

Cerebrovascular disease

Patients with a history of stroke or TIA are more likely to sustain a perioperative stroke.[80] [148] [159] Patients with significant but asymptomatic atheromatous disease in the extracranial cerebral arteries may be at increased risk on the grounds that they will be more vulnerable to regional ischaemia during periods of hypoperfusion. Although preoperative detection of a carotid bruit is associated with a two-fold increase in absolute perioperative stroke risk after CABS, it is a poor measure of the severity of stenosis and has been shown not to correlate well with angiographic findings.[37] In the presence of carotid disease detected by Doppler sonography, the risk of stroke is increased three-fold.[20] As expected, the risk of stroke increases with the severity of carotid disease. In a follow-up study of 4047 patients examined before CABS, Brener and colleagues demonstrated that in the presence of >50% carotid stenosis, the risk of stroke increased from 1.9% to 6.3%.[19] In 32 patients with complete carotid occlusion, the stroke rate was 15.6%.

In a study of 47 patients undergoing CABS at the Middlesex Hospital, studied with i.v. digital subtraction carotid angiography, 51% had evidence of atheroma and 17% had stenosis of at least one carotid artery in the neck.[57] The incidence of cognitive deficit at 8 days and 8 weeks after surgery was not significantly greater in those patients with angiographically visible carotid artery disease.

A retrospective study at the Cleveland Clinic revealed that the incidence of new stroke after open-heart surgery was 13.4% in 126 patients with previous stroke.[128] The likelihood of a new perioperative stroke was not related to the time interval between the previous stroke and surgery. Furthermore, the presence of extracranial occlusive disease appeared to be non-contributory. Patients who had had a stroke in the 3 months before surgery were more likely to have worsening of a prior deficit whereas those with a more remote history of stroke were more likely to have a stroke in a different brain region. Intraoperative hypotension was found to be more frequent in those patients with recent preoperative stroke, suggesting persistent haemodynamic vulnerability.

Current evidence suggests that asymptomatic extracranial cerebrovascular disease represents a modest increase in the risk of perioperative stroke, but other factors, such as embolism or hypoperfusion, are probably more important.

Diabetes mellitus and hyperglycaemia

For many years, the use of glucose-containing priming solutions in the extracorporeal circuit was commonplace. Although there is evidence that outcome from stroke in humans is worse in diabetics, there are no data unequivocally implicating hyperglycaemia as the cause.[138] The higher incidence of hypertension, renal impairment and vascular disease may partly explain a worse outcome in diabetic patients. In a study of 70 patients conducted at the Middlesex Hospital, allocated randomly to either electrolyte or dextrose prime, neuropsychological outcome was found to be worse in the latter group.[112] In a recent study using ^{133}Xe clearance, the Duke group demonstrated that insulin-dependent diabetic patients had impaired cerebral blood flow autoregulation, characterized by increased oxygen extraction, during CPB.[33] Several reports have suggested that diabetes mellitus is a risk factor for poor neurological outcome after CPB.[84 111 123]

In recent years, there has been a re-evaluation of the use of glucose-containing priming solutions in cardiac surgery.[139] On the grounds that hyperglycaemia appears to worsen neurological outcome in both focal and global cerebral ischaemia,[76 101] some investigators claim that hyperglycaemia during cardiac surgery is detrimental and should be avoided.[140] Others, however, suggest that glucose administration may be beneficial.[88 89]

In our experience, most centres avoid deliberate hyperglycaemia and treat intraoperative hyperglycaemia with insulin. The critical glucose concentration at which treatment should be instituted is unknown.

Genetic susceptibility

It is known that patients with similar physical characteristics, identical medical histories and cardiac disease of equivalent severity have markedly differing neurological and neuropsychological outcomes from uneventful cardiac surgery. This observation led investigators at Duke University to speculate that genetic factors may account for this variability.[105 106 155] Concurrent laboratory studies, focusing on apolipoprotein E, prompted a clinical investigation.

Apolipoprotein E (APOE), a 34 kD glycosylated lipid-binding protein, is expressed as three common isoforms (ε2, ε3 or ε4) in humans. Possession of the APOEε4 allele is now known to be a risk factor for the development of late-onset and sporadic forms of Alzheimer's disease.[129 130] It may also be associated with a worse outcome after subarachnoid haemorrhage[3] and increased severity of chronic neurological deficits in boxers exposed to chronic head trauma.[68] Interestingly, accelerated aortic atheromatous disease and early re-stenosis after coronary angioplasty, independent of serum cholesterol, may also be associated with APOEε4.[62]

APOE was evaluated as a predictor of postoperative cognitive dysfunction in 65 patients undergoing CABS.[155] A significant association was found between the APOEε4 allele and decline in four of nine measures of cognitive function at discharge from hospital and 6 weeks after surgery.

The notion that APOE isoforms may have a role in dictating the expression of early immediate genes after neuronal injury, and thus the balance between neuronal repair and neuronal death, is attractive but requires further investigation.

Education level, socioeconomic status and mood

An interesting observation is that a higher number of years of formal education appears to protect patients from cognitive decline.[106] Level of educational achievement however, correlates poorly with baseline (preoperative) cognitive function test scores.

Depression is commonly reported after cardiac surgery. The use of non-standard measures of depression, however, may have overestimated its frequency. A presumed association between postoperative depression and poor performance on psychometric tests has meant that mood assessment has become an integral component of many studies. In a recent study, the Center for Epidemiological Study of Depression (CES-D) depression questionnaire and a battery of neuropsychological tests were used to assess outcome in 124 CABS patients 1 month and 1 yr after surgery.[82] Depression was defined as a CES-D score >16. Only 12 (13%) patients not depressed before surgery were depressed 1 month afterwards, whereas 18 (53%) of those who were depressed before surgery were depressed at 1 month ($P=0.001$). One year after surgery, values were eight (9%) and 16 (47%), respectively ($P=0.001$). There was little or no correlation between depression and changes in cognitive function. The inference is that cardiac surgery neither causes nor cures depression.

Cerebral microembolization

Emboli, which may be gaseous or particulate, can be conveniently divided into 'macro' and 'micro' according to size. Macroemboli occlude flow in arteries 200 µm or greater in diameter, whereas microemboli occlude flow in small arteries, arterioles and capillaries.[14]

Air may reach the systemic circulation from the bypass circuit via the venous cannula, or as an inevitable consequence of left-heart surgery.[149] Not surprisingly, systemic embolization is more common during valve surgery than CABS.[72] The ultimate fate of bubbles depends on their initial size, the partial pressure of gases in solution and temperature, which dictates the solubility of gases in liquids. Because of high surface tension forces, small bubbles are unstable and tend to collapse. Bubbles are more likely to grow in size during rewarming when gas solubility decreases. Although bubbles are known to traverse the cerebral vasculature, they may cause endothelial injury.[14]

Particulate matter can also be categorized according to composition and origin. Biological particles arise from components of the circulation (aggregates of erythrocytes, leucocytes, platelets, denatured protein, fibrin) and the operative site (thrombus, fat, calcium, cellular aggregates, atheroma, valve debris, muscle fragments, hair). Non-biological particles arise from the extracorporeal circuit and cardiotomy reservoir (polyvinyl chloride, silicone rubber, antifoam, priming solutions, cardioplegia solutions) and from foreign material introduced into the operative field (fibres from swabs, glove talc, dust).

Considerable histological,[92] angiographic[13] and ultrasonographic[118 152] evidence suggests that cerebral embolization occurs in all patients subjected to CPB. Although it is not clear which types of microemboli cause most damage to the brain, a correlation between intraoperative cerebral microembolic load and postoperative neuropsychological dysfunction has been demonstrated.[28 119] The finding, in a recent animal study, that the use of cardiotomy suction was associated with histological evidence of increased cerebral microembolization suggests that blood aspirated from the surgical field can be a major source of microemboli.[23]

Aortic atheromatous disease

Although the possibility of atheromatous cerebral embolism during aortic surgery was recognized many years ago,[56] it is only in recent years that this problem has been revisited. The severity of aortic atheromatous disease increases sharply with age.[15] Postmortem studies indicate a prevalence of 20% in the fifth decade increasing to 80% in the eighth decade.[164] The prevalence of ulcerated aortic arch atheroma at autopsy has been shown to be higher (26% *vs* 5%) in patients with cerebrovascular disease but appears not to be correlated with the presence of extracranial internal carotid artery stenosis.[4] Surgical manipulations of the proximal aorta, cannulation through an atheromatous plaque or 'sandblasting' of the aortic wall during perfusion may cause atheroembolism. The advent of transoesophageal echocardiography (TOE) and intraoperative epiaortic ultrasonography has allowed a more detailed view of the aorta during surgery and quantification of atheromatous plaques according to thickness and the presence of mobile components.

The importance of aortic atheroembolism has been highlighted by Katz and colleagues[69] who found that the incidence of stroke was 25% in patients with a mobile plaque of the aortic arch compared with 2% in those with sessile plaque. A strong association between severe aortic atheroma and postoperative stroke or death has been confirmed by others.[8 38 59 123]

The successful use of intraoperative epicardial ultrasound in surgery for congenital heart lesions[160] stimulated use of the technique in adults.[10 99] Recent comparisons between intraoperative TOE and epiaortic ultrasound showed conclusively that TOE underestimated the presence and severity of aortic atherosclerosis.[39]

Several centres are currently investigating the efficacy of alterations in surgical technique based on ultrasonic evaluation of the aorta. Such alterations include aortic cannulation at a different site, avoidance of aortic cannulation altogether, avoidance of aortic cross clamping and replacement of the ascending aorta and/or aortic arch.

Duration of cardiopulmonary bypass

The suggestion that CPB is associated with progressive, embolic cerebral microvascular obstruction suggests a relationship between duration of bypass and adverse neurological outcome.[100 146] Many investigators have either observed or suggested that neurological outcome is related to the duration of bypass[18 45 83 162] while others have suggested otherwise.[53] The finding that progressive cerebral vasoconstriction leads to a gradual decrease in cerebral blood flow during prolonged non-pulsatile hypothermic bypass[117 127] may be an additional factor, but has not been substantiated.[36 132]

It is important to note that bypass time may be prolonged by several factors which may themselves contribute to cerebral injury. A slow (meticulous) or 'delayed' surgeon may occasionally increase bypass time. It is more usual, however, that complicated surgical procedures (e.g. combined valve and CABS), complications or technical problems (e.g. haemorrhage, aortic dissection) and difficulty weaning from bypass are the main causes of prolonged bypass. It is clear that all of these factors may reflect a greater severity of cardiac disease in a population of surgical patients that have a higher incidence of adverse neurological outcomes.

Perfusion: pressure, flow and pulsation

Few would doubt that prolonged periods of profound arterial hypotension *and* cerebral hypoperfusion are bad for the brain and that certain areas, at the boundaries of cerebral artery territories (so-called 'watersheds'), are particularly vulnerable.[45] The influence of systemic (arterial or 'pump') blood flow, flow character and cerebral perfusion pressure (CPP) on CBF during CPB and neurological outcome has been the subject of considerable debate.

In addition to pressure and flow, actual CBF during CPB is determined by other factors including: acid–base management strategy, temperature, depth of anaesthesia, packed cell volume and oxygen saturation.[132] During moderate hypothermia, cerebral autoregulation remains intact at a mean arterial pressure (MAP) as low as 30 mm Hg such that, in α-stat managed patients, CBF remains *virtually* constant within the range 30–100 mm Hg.[95] Children appear to tolerate a MAP as low as 15 mm Hg.[48] Recent evidence suggests that MAP in the range 51–75 mm Hg has a small effect on CBF during both hypothermic (+0.086 ml

100 g^{-1} min^{-1} mm Hg^{-1}) and normothermic (+0.178 ml 100 g^{-1} min^{-1} mm Hg^{-1}) CPB.[106 107] These findings are supported by the observation that at constant pump flow, jugular venous oxygen saturation (Sj_{O_2}) correlates with CPP during hypothermic, pulsatile CPB.[52]

Although maintenance of a perfusion pressure ≥50 mm Hg during hypothermic CPB appears to be tolerated by the majority of patients, the safety of this practice has been questioned.[24] The obvious question is, could higher perfusion pressures (i.e. ≥70 mm Hg) improve outcome?[58] In an attempt to answer the question, Gold and colleagues prospectively compared cardiac and neurological outcome variables in 248 patients undergoing elective CABS, allocated randomly to either lower (50–60 mm Hg) or higher (80–100 mm Hg) perfusion pressures.[46] Six months after surgery, the overall incidence of combined cardiac and neurological complications was significantly lower in the higher pressure group (4.8% *vs* 12.9%; $P=0.026$) as was the stroke rate (2.4% *vs* 7.2%). There were no differences in cognitive and functional outcomes. The small study population, unusually high baseline stroke rate (7.2%) and method of data analysis makes it hard to reach any definite conclusion.[70 121] The observed differences in outcome could have occurred by chance but may be accounted for by the greater number of patients with aortic atherosclerosis in the lower pressure group.

During CPB, systemic flow rate is usually based on body surface area and the degree of hypothermia (typically 1.6–2.4 litre min^{-1} m^{-2}) and adjusted according to indices of the adequacy of organ perfusion (e.g. arterial blood gases). Although it is well established that low pump flow with concomitant arterial hypotension results in decreased CBF, the independent effects of low flow and low pressure are less well characterized. In a baboon model of non-pulsatile hypothermic (28°C) CPB, Schwartz and colleagues showed that, regardless of pump flow, CBF was governed by mean arterial pressure (20–60 mm Hg). Furthermore, when mean arterial pressure was maintained constant, changes in pump flow (0.75–2.25 litre min^{-1} m^{-2}) did not alter CBF.[133] These findings are at odds with the results of several other studies of CBF during CPB.[47 125–127 147]

Govier and colleagues showed no correlation between CBF and either mean arterial pressure (30–110 mm Hg) or pump flow rate (1.0–2.2 litre min^{-1} m^{-2}) in 67 patients undergoing CABS.[47] In contrast, Soma and colleagues reported that CBF was directly dependent on pump flow rate (40–70 ml kg^{-1} min^{-1}).[147] The Bowman Gray group have reported the effects on CBF of alterations in arterial pressure with administration of sodium nitroprusside[126] and phenylephrine[127] (measured by ^{133}Xe clearance) at constant pump flow. In α-stat managed patients, changes in arterial pressure had no effect on CBF whereas in pH-stat managed patients, CBF was correlated positively with pressure. A subsequent study showed that modest changes in pump flow rate (1.75–2.25 litre min^{-1} m^{-2}) had no influence on arterial pressure or CBF.[125]

Non-pulsatile perfusion is associated with diminished endothelial shear stress and a reduction in endothelial nitric oxide production leading to increased vascular resistance and end-organ dysfunction.[77] Furthermore, it is suggested that non-pulsatile flow may cause stasis of cerebral interstitial fluid[167] and also the cerebral swelling demonstrated after hypothermic[54] and normothermic[55] bypass. In a canine model of extracorporeal perfusion after 15 min of cardiac arrest, non-pulsatile perfusion was associated with worse cerebral hyperaemia and lower oxygen consumption compared with pulsatile perfusion.[5] In a prospective study of 316 patients undergoing CABS, however, Murkin and colleagues were unable to demonstrate any influence of mode of perfusion on neurobehavioural outcome.[96]

Despite considerable research, the characteristics of 'optimal' CPB perfusion remain to be defined. Within the bounds of usual CPB conduct, pressure, flow and flow character appear to have little influence on CBF.[132] In the absence of unequivocal evidence suggesting otherwise, there seems little reason to alter perfusion practices that are tolerated by the vast majority of patients.

Temperature

Since the early days of cardiac surgery, systemic and regional hypothermia has been the mainstay of organ protection during CPB. Hypothermia is unique among neuroprotective modalities in that it reduces energy consumption (about 7% per °C) associated with both electrophysiological function and maintenance of cellular integrity. At modest hypothermia, autoregulation of CBF is such that CBF is tightly coupled to cerebral metabolic rate ($CMRo_2$). With decreasing temperature, the CBF:$CMRo_2$ ratio increases resulting in 'luxury' brain blood flow. At temperatures of 15–20°C (deep hypothermia), pressure–flow autoregulation is lost. In animal models of cerebral ischaemia, mild hypothermia reduces neuronal adenosine triphosphate (ATP) depletion,[169] and both delays the onset and reduces the rate of excitatory amino acid release.[102]

Hypothermia does, however, have several distinct disadvantages, not least of which is the requirement for rewarming the patient at the end of the procedure. Placement of the arterial cannula in the ascending aorta results in cerebral perfusion with blood at a temperature close to that of blood leaving the heat-exchanger. For this reason it is easy to produce inadvertent cerebral hyperthermia during rewarming. The observation that warming from moderate hypothermic CPB is associated with jugular venous desaturation (Sj_{O_2} <50%) suggests that cerebral oxygen extraction during this period exceeds supply.[29 34] In a series of 255 patients studied at Duke University, the cerebral arteriovenous oxygen difference (Ca_{O_2}–Cv_{O_2}) on rewarming was significantly associated with overall cognitive decline ($P=0.0013$).[35]

Rapid rates of warming, using temperatures >41°C, have long been considered a potential cause of neurological injury during CPB.[22] Hyperthermia increases $CMRo_2$ and may cause protein denaturation and air embolism, in addition to tissue ischaemia.[30] In a recent study, nasopharyngeal temperature (T_{NP}) monitoring was compared with continuous jugular venous temperature monitoring.[51] Although there was a high degree of precision between the two monitoring sites, there was a marked difference in bias. This was most pronounced during rewarming when jugular venous temperature was 3.4°C higher than T_{NP}. The authors concluded that T_{NP} monitoring underestimated brain temperature during rewarming and speculated that as a result, the brain may be at increased risk of neurological injury. However, in an unrandomized and unblinded study of 28 CABS patients, von Knobelsdorff and colleagues suggested that the use of a 'slow' rewarming regimen did not attenuate reductions in Sj_{O_2}.[163] An accompanying editorial raised several methodological issues and advised caution in interpreting these findings.[110]

The finding that even mild hyperthermia (38–39°C) increases excitotoxic neurotransmitter release during cerebral hypoxia and delays recovery of energy metabolism is cause for concern.[93] The use of mild hypothermia (34°C) after CPB and in the early postoperative period has been shown not to be associated with increased bleeding, cardiac morbidity or time to tracheal extubation.[103] Any neuroprotective effect of this strategy remains to be established in prospective, randomized studies.

In recent years, studies have suggested that normothermic cardioplegia may improve myocardial protection during heart operations.[93] As interest in these so-called 'warm-heart' techniques has increased, their use has become widespread. The immediate concern was that abandonment of hypothermic perfusion during CPB would compromise cerebral protection and lead to a higher incidence of neurological morbidity.

To date, studies that have examined the effect of normothermic cardioplegia and CPB on myocardial and neurological outcome have yielded conflicting results. Singh and colleagues,[142 143] the Warm Heart Investigators[165] and McLean and colleagues[86] reported no increase in neurological complications. Martin and colleagues[79] however, demonstrated a marked increase in neurological injury in patients maintained at normothermia during CPB. Directly comparing these studies is difficult because actual brain temperature was not measured and small variations in the conduct of CPB and operative technique may have had a crucial influence on temperature. This is further confounded by relatively low mean patient ages and the deliberate exclusion of patients with increased risk of perioperative stroke.

In an attempt to resolve the issue, Mora and colleagues[93] compared neurological and neuropsychological outcomes in 138 patients allocated randomly to receive either intermittent cold oxygenated crystalloid cardioplegia during hypothermic (≤28°C) bypass or continuous retrograde normothermic blood cardioplegia during normothermic (≥35°C) bypass. All seven patients found to have new focal neurological deficits came from the normothermic group. One patient died as a result of cerebral infarction. In contrast, there were no significant differences in neurocognitive test performances, although the study was not sufficiently powered to detect a difference.

Hypothermic neuroprotection is consistent with the findings of Regragui and colleagues[120] who prospectively investigated the effect of perfusion temperature (28°C, 32°C or 37°C) on postoperative cognitive function in 96 adults undergoing elective CABS with CPB. Compared with patients perfused at 32°C, the incidence of cognitive deficits was significantly higher in patients perfused at 37°C ($P=0.021$). Cooling to 28°C appeared to offer no additional benefit.

Despite suggestions that normothermic bypass does not increase risk,[85] it is interesting to note that at a meeting of researchers in the field, held in Oxford at the end of 1996, the majority of participants indicated that they would rather undergo hypothermic (32°C), rather than normothermic, bypass if they required cardiac surgery (personal communication)!

Acid–base management

The importance of maintaining normocapnia before the onset of CPB was highlighted by Nevin and colleagues in 1987. Three days after surgery, patients who had been inadvertently hyperventilated ($Pa_{CO_2} \leq 4.7$ kPa) had a higher incidence of neurological (46% *vs* 27%) and psychometric (71% *vs* 40%) deficits than patients who were normocapnic (Pa_{CO_2} 4.7–6.0 kPa).[104]

The solubility of gases in a liquid, including blood, increases as temperature decreases. When arterial blood gases are analysed with a temperature correction during hypothermia, patients appear to have a respiratory alkalosis (decreased Pa_{CO_2} and increased pH). Addition of carbon dioxide to 'normalize' Pa_{CO_2} and maintain a pH of 7.40 is known as 'pH-stat' acid–base management. The use of arterial blood gases without temperature correction is known as 'α-stat' management.

During moderate hypothermic CPB, pressure–flow autoregulation of CBF is maintained when α-stat blood-gas management is used but lost when pH-stat management is used. The inability to autoregulate CBF at low perfusion pressures, the possibility of 'steal' in patients with intracranial cerebrovascular disease and the presence of 'acidosis' during rewarming associated with the pH-stat strategy increase the potential for brain injury. Furthermore, the excessive CBF associated with pH-stat may substantially increase the delivery of emboli to the brain.[94]

The influence of pH management has been assessed by several groups. In a study of 86 patients undergoing CABS, Bashein and colleagues reported that the pH management strategy had no influence on either cardiac or neurocognitive outcome.[11] Stephan and colleagues, in a prospective, randomized study of 65 patients undergoing CABS with hypothermic (26°C) CPB, reported that use of the pH-stat strategy was associated with cerebral hyperaemia (+191% *vs* –18%) and a higher incidence of neurological dysfunction 7 days after surgery (P=0.036).[150] In a study of 316 patients undergoing CABS, cognitive dysfunction at 2 months was less prevalent after 90 min of CPB in patients managed with α-stat than with the pH-stat strategy (27% *vs* 44%; P=0.047).[96] Similar findings have been reported in a study of 70 patients undergoing CABS at St Thomas' Hospital (20% *vs* 48.6%; P<0.05).[161]

In patients[66] and animals[6 71] undergoing deep hypothermic cardiac arrest (DHCA) however, pH-stat management before the onset of circulation arrest appears to improve neurological outcome. Using magnetic resonance spectroscopy in an immature piglet model of DHCA, Aoki and colleagues have shown that recovery of cerebral ATP and intracellular pH in the initial 30 min of reperfusion is faster in pH-stat managed animals.[6] In α-stat managed animals, cerebral intracellular pH decreased during early reperfusion, whereas it showed continuous recovery in pH-stat managed animals. Postoperative brain water content (oedema) was also significantly lower in pH-stat managed animals. Possible reasons for these observations include improved brain cooling by increased blood flow to subcortical areas, improved oxygen delivery and reduction of reperfusion injury, in addition to an alkaline shift in intracellular pH with hypothermia in spite of a stable blood pH.[6]

Neuroprotective interventions

It is clear that risk factors for adverse neurological outcome fall into two categories: those that cannot be modified (i.e. age, sex, genotype and medical history) and those that may (i.e. cerebral embolism, aortic atheroma, CPB duration and cerebral perfusion). Interventions designed to reduce or prevent neurological injury during cardiac surgery can be divided into two categories: (1) physical and (2) pharmacological. Table 5 summarizes some of the physical interventions that have been used or advocated.

Pharmacological interventions

A greater understanding of the pathophysiology of neurological injury offers the hope of pharmacological neuroprotection. At present, however, there is no agreement on the need for prophylactic neuroprotectants in cardiac surgery, much less the choice of drug.[122 124]

With the exception of some anaesthetic drugs, many of the prototype neuroprotective agents studied in cardiac surgery were developed originally for the treatment of stroke. In many ways, cardiac surgery is a convenient model with which to test these agents—a large number of patients sustaining a cerebral injury at a predictable time. Unfortunately, disagreement over the precise nature of heart surgery related brain injury (focal *vs* diffuse 'micro-focal' *vs* diffuse), the confounding influences of other 'standard' neuroprotective strategies (hypothermia, blood-gas management, arterial line filtration, etc.) and the lack of a gold standard for assessment of neurological and cognitive outcomes, reduces its use as an experimental model.

The observation that certain barbiturates could reduce $CMRo_2$ led to extensive research into their neuroprotective potential. In 1986, Nussmeier, Arlund and Slogoff were first to report barbiturate neuroprotection in humans.[114] One hundred and eighty-two patients undergoing open-ventricle procedures were randomized to either thiopental (an initial bolus followed by a continuous infusion—mean total dose 39.5 mg kg^{-1}), sufficient to maintain electroencephalographic silence throughout the period from before aortic cannulation to termination of bypass (n=89) or fentanyl (n=93). On the first postoperative day, clinical neuropsychiatric abnormalities were found to be more common in the control group (5.6% *vs* 8.6%). By day 10 after operation, all neuropsychiatric dysfunction had resolved in the thiopental group but persisted in seven (7.5%) control patients (P<0.025). The incidence of complications was related significantly to calcification of replaced valves, aortic valve replacement, advanced age and prolonged bypass, but not to hypotension during perfusion. It is curious to note that in a later publication by the same group, the background incidence of new neurological deficit was much lower.[90 144] In a similar study of patients undergoing CABS, however, no protective effect could be demonstrated.[170] Mortality in the thiopental; group was, however, lower than in controls (0.7% *vs* 2.6%; P=0.018). More recently, a retrospective evaluation of 227 open-heart surgery patients revealed that thiopental (mean dose 38.1 mg kg^{-1}) had no beneficial effect on neurological outcome although mortality was significantly lower in the thiopental group (1.2% *vs* 9.6%; P=0.034).[115]

Propofol has similar effects to thiopental on $CMRo_2$ and CBF.[26] Although *in vitro* evidence suggests a direct neuroprotective action, perhaps via $GABA_A$ receptors,[63] it is suggested that a propofol-induced reduction in CBF reduces the delivery of microemboli to the cerebral circulation.[109]

Calcium channel antagonists have stimulated considerable research. Of these, nimodipine, an L-type calcium channel blocker, has shown considerable promise in the management of subarachnoid haemorrhage[116] but not acute head injury.[157] A prospective, double-blind, randomized study of nimodipine in 400 patients undergoing valve surgery was terminated because of lack of efficacy and significant adverse events.[75] The incidence of new neurological deficits was no different to placebo (72% *vs* 77%; P=0.55). In the 6-month follow-up period, mortality was significantly higher in the nimodipine group (10.7% *vs* 1.3%; P=0.02). Major haemorrhage was also significantly more common in the nimodipine group (13.3% *vs* 4 1%; P=0.04).

Prostacyclin has been used in addition to, or as a replacement for, heparin during CPB. It is known to reduce platelet aggregation during extracorporeal circulation and may therefore be neuroprotective.[42] In 1987, Fish and

Table 5 Potentially neuroprotective physical interventions in cardiac surgery

General considerations	Expeditious surgery
	Attention to myocardial preservation and haemostasis
Maintaining cerebral perfusion	Avoid prolonged/profound arterial hypotension
	Avoid prolonged systemic hypoperfusion
	Avoid prolonged superior vena caval obstruction
	Consider retrograde cerebral perfusion during DHCA
Reducing cerebral embolization	Adequate anticoagulation
	Minimize aortic manipulation/instrumentation
	Careful (de)cannulation of the aorta
	Avoid venous air entrainment
	Use of arterial line filter
	Avoid CPB altogether (i.e. 'beating heart' procedures)
	Use of exhaustive deairing/debridement procedures
	Avoid or reduce use of cardiotomy suction
	Consider heparin-bonded circuits
Temperature management	Moderate hypothermia (i e 32°C)
	Avoid rapid/excessive rewarming
Acid–base management	Alpha-stat regimen (pH-stat during cooling before DHCA and in patients with significant aorto-pulmonary anastomoses)
	Avoid hypercapnia and hypocapnia
Other	Avoid/treat hyperglycaemia
Advanced neurological monitoring	Jugular venous oxygen saturation
	Near infrared spectroscopy (NIRS)
	Electroencephalography (EEG)
	Transcranial Doppler sonography

colleagues reported the results of a randomized, double-blind study designed to evaluate the effect of prostacyclin on the incidence and severity of postoperative neuropsychological dysfunction in 100 patients undergoing CABS.[41] Of 96 patients who completed the psychological and neurological evaluations 1 week after surgery, 74 were evaluated psychologically 2 months after surgery. There were no differences in neurological outcome or psychological test performance.

Grieco and colleagues have recently reported the results of a double-blind, placebo-controlled pilot study of GM_1 ganglioside in patients undergoing cardiac surgery.[49] Although there was a trend towards improved neurological and neuropsychological outcome in the ganglioside treated group, the differences did not reach statistical significance.

The systemic inflammatory response associated with CPB, characterized by the release of cytokines in response to activation of the coagulation, fibrinolytic and complement cascades, has been the subject of recent discussion.[60] The bovine serine protease inhibitor, aprotinin, has been shown to significantly reduce intraoperative bleeding and transfusion requirements in a variety of settings, including cardiac surgery with CPB. Despite an early report suggesting an increased incidence in perioperative myocardial infarction[31] there is now a suggestion, from a meta-analysis of several studies, that high-dose aprotinin may actually reduce the incidence of perioperative stroke.[145] Whether or not this action is a result of the non-specific anti-inflammatory properties of antiproteases remains unclear. Nafamostat mesilate (FUT-175), a synthetic serine protease inhibitor, is currently under investigation in cardiac surgery. Although it is known that glucocorticoids can suppress some of the inflammatory cytokines liberated during CPB,[61] recent laboratory evidence suggests that they may worsen neurological outcome.[81]

Indications that free radical production increases during CPB[9] [64] and in cerebral ischaemia[27] suggests a possible neuroprotective role for free radical scavengers.[25] Desferrioxamine, which may reduce iron-catalysed free radical production, has been evaluated in 24 adult patients (12 controls, 12 treated) undergoing CPB for various cardiac operations.[87] Desferrioxamine was given both i.v. and with the cardioplegic solution. Polymorphonuclear neutrophils (PMN) harvested from desferrioxamine-treated patients produced significantly fewer superoxide radicals than those of control patients. It was concluded that desferrioxamine-exposed PMN had decreased oxidative responsiveness. These results were thought to be consistent with the hypothesis that desferrioxamine reduces free radical-mediated amplification of the inflammatory response to CPB. Although this could be effective in reducing the harmful effects of extracorporeal circulation, no evaluation of any neuroprotective effect has been reported.

In light of experimental evidence indicating a role for excitatory amino acid neurotransmission in the pathogenesis of brain injury occurring during cardiac surgery with CPB, several compounds have reached phase II clinical trials. Of these, the competitive glutamate antagonist, remacemide hydrochloride, has been shown to improve neuropsychological outcome in a prospective, randomized, double-blind study in patients undergoing CABS.[7] Compared with the placebo group, patients treated with remacemide showed significantly superior performance on three of 10 neuropsychological tests. Furthermore, the remacemide group had significantly greater improvement in performance on a composite measure (total z score) of neuropsychological performance (P=0.028).

Numerous drugs are currently being evaluated in stroke, epilepsy, head injury, subarachnoid haemorrhage and cardiac arrest. Putative neuroprotective drugs currently under investigation in cardiac surgery include chlormethiazole, lidocaine, nicorandil and magnesium sulphate.

Summary

The neurological complications of cardiac surgery are associated with significantly increased mortality, morbidity and resource utilization. The use of new surgical techniques, introduction of wider indications for surgery and increased public expectation has led to an increase in the average age of cardiac surgical patients and an increased incidence of repeat procedures. With these changes has come an increased risk of neurological complications.

The likelihood of perioperative stroke varies between 1% and 5% in most published series and is dependent on a multitude of risk factors. Of these, patient age, aortic atheroma, symptomatic cerebrovascular disease, diabetes mellitus and the type of surgery appear to be most important. Cognitive deterioration after cardiac surgery is far more common, affecting as many as 80% of patients a few days after surgery and persisting in one-third. Despite an increase in the age of the cardiac surgical population, the reported incidence of cognitive dysfunction after cardiac surgery seems to have fallen in recent years. Whether this is a real phenomenon or the result of changes in the use of psychometric testing and the definition of cognitive decline remains unclear.

Recognition that certain equipment, surgical practices and patient factors contribute to neurological morbidity has prompted 'neuroprotective' interventions. Some of these (e.g. arterial line filtration and α-stat management) have been shown to improve outcome. Despite these measures, a small number of patients will inevitably sustain cerebral injury during otherwise successful cardiac surgery. Although pharmacological neuroprotection may, in the future, offer some of these patients an improved outcome, it is unlikely that any single agent will prevent neurological injury. In the meantime, the CNS complications of cardiac surgery remain a fertile area of research.

Acknowledgements

We gratefully acknowledge the support of the National Institutes of Health, National Institute on Aging, Claude D. Pepper Older Americans Independence Center, No. 5 P60-AG-11268; National Institutes of Health Grant RO1-AG-09663; National Institutes of Health Leadership and Excellence Award No. 5 R35-AG-07922; National Institutes of Health Alzheimer's Disease Research Center No 5 P50-AG-05128, National Institutes of Health Grant 1RO3-AG-14194–01; National Institutes of Health Grant 1RO1-HL-54316–01; American Heart Association Grant-In-Aid 95010970; The Lord Amulree Traveling Studentship (UCH); and a grant from the Anesthesia Patient Safety Foundation

References

1 Åberg T, Ronquist G, Tydén H, *et al.* Adverse effects on the brain in cardiac operations as assessed by biochemical, psychometric, and radiologic methods. *J Thorac Cardiovasc Surg* 1984; **87**: 99–105

2 Åberg T, Ronquist G, Tydén H, Åhlund P, Bergstrom K. Release of adenylate kinase into cerebrospinal fluid during open-heart surgery and its relation to postoperative intellectual function. *Lancet* 1982; **i**: 1139–42

3 Alberts MJ, Graffagnino C, McClenny C, *et al.* ApoE genotype and survival from intracerebral haemorrhage. *Lancet* 1995; **346**: 575

4 Amarenco P, Duyckaerts C, Tzourio C, Henin D, Bousser MG, Hauw JJ. The prevalence of ulcerated plaques in the aortic arch in patients with stroke. *New Engl J Med* 1992; **326**: 221–5

5 Anstadt MP, Tedder M, Hegde SS, *et al.* Pulsatile versus nonpulsatile reperfusion improves cerebral blood flow after cardiac arrest. *Ann Thorac Surg* 1993, **56**: 453–61

6 Aoki M, Nomura F, Stromski ME, *et al.* Effects of pH on brain energetics after hypothermic circulatory arrest. *Ann Thorac Surg* 1993; **55**: 1093–103

7 Arrowsmith JE, Harrison MJG, Newman SP, Stygall J, Timberlake N, Pugsley WB. Neuroprotection of the brain during cardiopulmonary bypass: a randomised trial of remacemide during coronary artery bypass in 177 patients. *Stroke* 1998; **29**. 2357–62

8 Barbut D, Lo YW, Hartman GS, *et al.* Aortic atheroma is related to outcome but not numbers of emboli during coronary bypass *Ann Thorac Surg* 1997; **64**: 454–9

9 Barsacchi R, Pelosi G, Maffei S, *et al.* Myocardial vitamin E is consumed during cardiopulmonary bypass: indirect evidence of free radical generation in human ischemic heart. *Int J Cardiol* 1992; **37**: 339–43

10 Barzilai BB, Marshell WG, Saffitz JE, Kouchoukos N. Avoidance of embolic complications by ultrasound characterization of the ascending aorta. *Circulation* 1989; **80**: I-275–9

11 Bashein G, Townes B, Nessly M, *et al.* A randomised trial of carbon dioxide management during hypothermic cardiopulmonary bypass. *Anesthesiology* 1990, **72**: 7–15

12 Blachly PH, Kloster FE. Relation of cardiac output to post-cardiotomy delirium. *J Thorac Cardiovasc Surg* 1966; **52**: 422–7

13 Blauth C, Arnold J, Kohner EM, Taylor KM. Retinal microembolism during cardiopulmonary bypass demonstrated by fluorescein angiography. *Lancet* 1986; **ii**: 837–9

14 Blauth CI. Macroemboli and microemboli during cardiopulmonary bypass. *Ann Thorac Surg* 1995; **59**: 1300–3

15 Blauth CI, Cosgrove DM, Webb BW, *et al.* Atheroembolism from the ascending aorta. An emerging problem in cardiac surgery. *J Thorac Cardiovasc Surg* 1992; **103**: 1104–12

16 Blumenthal JA, Mhanna EP, Madeen DJ. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. *Ann Thorac Surg* 1995; **59**: 1345–50

17 Borowicz LM, Goldsborough MA, Selnes OA, McKhann GM. Neuropsychologic change after cardiac surgery. a critical review. *J Cardiothorac Vasc Anesth* 1996; **10**: 105–11

18 Branthwaite MA. Neurological damage related to open-heart surgery. A clinical survey. *Thorax* 1972; **27**· 748–53

19 Brener BJ, Brief DK, Alpert J, Goldenkranz RJ, Parsonnet V. The risk of stroke in patients with asymptomatic carotid stenosis undergoing cardiac surgery: a follow-up study. *J Vasc Surg* 1987; **5**: 269–79

20 Breslau PJ, Fell G, Ivey TD, Bailey WW, Miller DW, Strandness DE. Carotid arterial disease in patients undergoing coronary artery bypass operations. *J Thorac Cardiovasc Surg* 1981; **82**: 765–7

21 Breuer AC, Furlan AJ, Hanson MR, *et al.* Central nervous system complications of coronary artery bypass graft surgery: prospective analysis of 421 patients. *Stroke* 1983; **14**: 682–7

22 Brierley JB. Neuropathological findings in patients dying after open-heart surgery. *Thorax* 1963; **18**: 291–304

23 Brooker RF, Brown WR, Moody DM, *et al.* Cardiotomy suction: a major source of brain lipid emboli during cardiopulmonary bypass. *Ann Thorac Surg* 1998; **65**: 1651–5

24 Cartwright CR, Mora Mangano C. Con: During cardiopulmonary bypass for elective coronary artery bypass grafting, perfusion pressure should not routinely be greater than 70 mmHg. *J Cardiothorac Vasc Anesth* 1998; **12**: 361–4

25 Cavarocchi NC, England MD, O'Brien JF, *et al.* Superoxide generation during cardiopulmonary bypass: is there a role for vitamin E? *J Surg Res* 1986; **40**: 519–27

26 Cheng MA, Theard MA, Tempelhoff R. Intravenous agents and intraoperative neuroprotection. Beyond barbiturates. *Crit Care Clin* 1997; **13**: 185–99

27 Chow HS, Lynch JJ III, Rose K, Choi DW. Trolox attenuates cortical neuronal injury induced by iron, ultraviolet light, glucose deprivation, or AMPA. *Brain Res* 1994; **639**: 102–8

28 Clark RE, Brillman J, Davis DA, Lovell MR, Price TRP, Magovern GJ. Microemboli during coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1995; **109**: 249–58

29 Cook DJ, Oliver WC Jr, Orszulak TA, Daly RC. A prospective, randomized comparison of cerebral venous oxygen saturation during normothermic and hypothermic cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1994; **107**: 1020–8

30 Cook DJ, Orszulak TA, Daly RC, Buda DA. Cerebral hyperthermia during cardiopulmonary bypass in adults. *J Thorac Cardiovasc Surg* 1996; **111**: 268–9

31 Cosgrove DM, Heric B, Lytle BW, et *al.* Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. *Ann Thorac Surg* 1992; **54**: 1031–6

32 Cosgrove DM, Loop FD, Lytle BW, *et al.* Primary myocardial revascularisation. *J Thorac Cardiovasc Surg* 1984; **88**: 673–84

33 Croughwell N, Lyth M, Quill TJ, et *al.* Diabetic patients have abnormal cerebral autoregulation during cardiopulmonary bypass. *Circulation* 1990; **82**: IV407–12

34 Croughwell ND, Frasco P, Blumenthal JA, Leone BJ, White WD, Reves JG. Warming during cardiopulmonary bypass is associated with jugular bulb desaturation. *Ann Thorac Surg* 1992; **53**: 827–32

35 Croughwell ND, Newman MF, Blumenthal JA, *et al.* Jugular bulb saturation and cognitive dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1994; **58**: 1702–8

36 Croughwell ND, Reves JG, White WD, et *al.* Cardiopulmonary bypass time does not affect cerebral blood flow. *Ann Thorac Surg* 1998; **65**: 1226–30

37 David TE, Humphries AW, Young JR. A correlation of neck bruits and arteriosclerotic carotid arteries. *Arch Surg* 1973; **107**: 729–31

38 Dávila-Román VG, Barzilai B, Wareing TH, Murphy SF, Kouchoukos NT. Intraoperative ultrasonographic evaluation of the ascending aorta in 100 consecutive patients undergoing cardiac surgery. *Circulation* 1991; **84**: II47–53

39 Dávila-Román VG, Phillips KJ, Daily BB, Davila RM, Kouchoukos NT, Barzilai B. Intraoperative transesophageal echocardiography and epiaortic ultrasound for assessment of atherosclerosis of the thoracic aorta. *J Am Coll Cardiol* 1996; **28**: 942–7

40 Dodds C, Allison J. Postoperative cognitive deficit in the elderly surgical patient. *Br J Anaesth* 1998; **81**: 449–62

41 Fish KJ, Helms KN, Sarnquist FH, *et al.* A prospective, randomized study of the effects of prostacyclin on neuropsychologic dysfunction after coronary artery operation. *J Thorac Cardiovasc Surg* 1987; **93**: 609–15

42 Fish KJ, Sarnquist FH, van Steennis C, et *al.* A prospective, randomized study of the effects of prostacyclin on platelets and blood loss during coronary bypass operations. *J Thorac Cardiovasc Surg* 1986; **91**: 436–42

43 Gardner TJ, Horneffer PJ, Gott VL, *et al.* Coronary artery bypass grafting in women. A ten year perspective. *Ann Surg* 1985; **201**: 780–4

44 Gardner TJ, Horneffer PJ, Manolio TA, *et al.* Stroke following coronary artery bypass grafting: a ten-year study. *Ann Thorac Surg* 1985; **40**: 574–81

45 Gilman S. Cerebral disorders after open-heart operations. *New Engl J Med* 1965; **272**: 490–8

46 Gold JP, Charlson ME, Williams-Russo P, *et al.* Improvement of outcomes after coronary artery bypass. A randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg* 1995; **110**: 1302–11

47 Govier AV, Reves JG, McKay RD, et *al.* Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass. *Ann Thorac Surg* 1984; **38**: 592–600

48 Greeley W, Ungerleider R, Kern F, Brusino F, Smith L, Reves J. Effects of cardiopulmonary bypass on cerebral blood flow in neonates, infants and children. *Circulation* 1989; **80**: I209–15

49 Grieco G, d'Hollosy M, Culliford AT, Jonas S. Evaluating neuroprotective agents for clinical anti-ischemic benefit using neurological and neuropsychological changes after cardiac surgery under cardiopulmonary bypass. Methodological strategies and results of a double-blind, placebo-controlled trial of GM1 ganglioside. *Stroke* 1996; **27**: 858–74

50 Grocott HP, Croughwell ND, Amory DW, Newman MF. Cerebral emboli and serum S100β during cardiac surgery. *Ann Thorac Surg* 1998; **65**: 1645–9

51 Grocott HP, Newman MF, Croughwell ND, White WD, Lowry E, Reves JG. Continuous jugular venous versus nasopharyngeal temperature monitoring during hypothermic cardiopulmonary bypass for cardiac surgery *J Clin Anesth* 1997; **9**: 312–16

52 Grubhofer G, Lassnigg AM, Schneider B, Rajek MA, Pernerstorfer T, Hiesmayr MJ. Jugular venous bulb oxygen saturation depends on blood pressure during cardiopulmonary bypass. *Ann Thorac Surg* 1998; **65**: 653–7

53 Hammeke TA, Hastings JE. Neuropsychologic alterations after cardiac operation. *J Thorac Cardiovasc Surg* 1988; **96**: 326–31

54 Harris DN, Bailey SM, Smith PL, Taylor KM, Oatridge A, Bydder GM. Brain swelling in first hour after coronary artery bypass surgery. *Lancet* 1993; **342**: 586–7

55 Harris DN, Oatridge A, Dob D, Smith PL, Taylor KM, Bydder GM. Cerebral swelling after normothermic cardiopulmonary bypass. *Anesthesiology* 1998; **88**: 340–5

56 Harris LS, Kennedy JH. Atheromatous cerebral embolism. A complication of surgery of the thoracic aorta. *Ann Thorac Surg* 1967; **4**: 319–26

57 Harrison MJ, Schneidau A, Ho R, Smith PL, Newman S, Treasure T. Cerebrovascular disease and functional outcome after coronary artery bypass surgery. *Stroke* 1989; **20**: 235–7

58 Hartman G. Pro: During cardiopulmonary bypass for elective coronary artery bypass grafting, perfusion pressure should routinely be greater than 70 mmHg. *J Cardiothorac Vasc Anesth* 1998; **12**: 358–60

59 Hartman GS, Yao FSF, Bruefach M, *et al.* Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study. *Anesth Analg* 1996; **83**: 701–8

60 Hill GE. The inflammatory response to cardiopulmonary bypass. *Int Anesthesiol Clin* 1996; **34**: 95–108

61 Hill GE, Alonso A, Spurzem JR, Stammers AH, Robbins RA. Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans. *J Thorac Cardiovasc Surg* 1995; **110**: 1658–62

62 Hixson JE Apolipoprotein E polymorphisms affect atherosclerosis in young males. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group *Arterioscler Thromb* 1991; **11**: 1237–44

63 Hollrigel GS, Toth K, Soltesz I. Neuroprotection by propofol in acute mechanical injury: role of GABAergic inhibition. *J Neurophysiol* 1996; **76**: 2412–22

64 Inal M, Alatas O, Kural T, Sevin B. Oxygen free radicals in erythrocytes during open heart operation. *J Cardiovasc Surg* 1994; **35**: 147–50

65 Jacobs AK, Kelsey SF, Mori Brooks M, *et al.* Better outcome for women compared with men undergoing coronary revascularization. A report from the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1998; **98**· 1279–85

66 Jonas RA. Hypothermia, circulatory arrest, and the pediatric brain. *J Cardiothorac Vasc Anesth* 1996; **10**: 66–74

67 Jones EL, Weintraub WS, Craver JM, Guyton RA, Cohen CL. Coronary bypass surgery. is the operation different today? *J Thorac Cardiovasc Surg* 1991; **101**: 108–15

68 Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. *JAMA* 1997; **278**: 136–40

69 Katz ES, Tunick PA, Rusinek H, Ribakove G, Spencer FC, Kronzon K. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *J Am Coll Cardiol* 1992; **104**: 70–7

70 Keats AS, Slogoff S. Perfusion pressure and coronary bypass. *J Thorac Cardiovasc Surg* 1996; **112**: 204–6

71 Kirshbom PM, Skaryak LR, DiBernardo LR, *et al.* pH-stat cooling improves cerebral metabolic recovery after circulatory arrest in a piglet model of aortopulmonary collaterals. *J Thorac Cardiovasc Surg* 1996; **111**· 147–55

72 Kuroda Y, Uchimoto R, Kaieda R, *et al.* Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. *Anesth Analg* 1993; **76**: 222–7

73 Laskowitz DT, Grocott HP, Hsia A, Copeland KR Serum markers of cerebral ischemia. *J Stroke Cerebrovasc Dis* 1998, **7**. 234–41

74 Lee WH, Brady MP, Rowe JM, Miller WC. Effects of extracorporeal circulation upon behavior, personality, and brain function. Part II, hemodynamic, metabolic, and psychometric correlations. *Ann Surg* 1971; **173**: 1013–23

75 Legault C, Furberg CD, Wagenknecht LE, *et al.* Nimodipine neuroprotection in cardiac valve replacement: report of an early terminated trial. *Stroke* 1996; **27**· 593–8

76 Li PA, Kristian T, Shamloo M, Siesjo BK. Effects of preischemic hyperglycemia on brain damage incurred by rats subjected to 2.5 or 5 minutes of forebrain ischemia. *Stroke* 1996; **27**. 1592–602

77 Macha M, Yamazaki K, Gordon LM, *et al.* The vasoregulatory role of endothelium derived nitric oxide during pulsatile cardiopulmonary bypass. *ASAIO J* 1996; **42**. M800–4

78 Mahanna EP, Blumenthal JA, White WD, *et al* Defining neuropsychological dysfunction after coronary bypass grafting. *Ann Thorac Surg* 1996; **61**: 1342–7

79 Martin TC, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT. Prospective, randomized trial of retrograde warm-blood cardioplegia: myocardial benefit and neurologic threat. *Ann Thorac Surg* 1994; **57**. 298–304

80 Martin WR, Hashimoto SA Stroke in coronary bypass surgery *Can J Neurol Sci* 1982; **9**: 21–6

81 McIntosh LJ, Sapolsky RM. Glucocorticoids may enhance oxygen radical-mediated neurotoxicity *Neurotoxicology* 1996; **17**: 873–82

82 McKhann GM, Borowicz LM, Goldsborough MA, Enger C, Selnes OA Depression and cognitive decline after coronary artery bypass grafting. *Lancet* 1997; **349**: 1282–4

83 McKhann GM, Goldsborough MA, Borowicz LM Jr, *et al.* Predictors of stroke risk in coronary artery bypass patients. *Ann Thorac Surg* 1997; **63**: 516–21

84 McKhann GM, Goldsborough MA, Borowicz LM Jr, *et al.* Cognitive outcome after coronary artery bypass: a one-year prospective study. *Ann Thorac Surg* 1997, **63**· 510–15

85 McLean RF, Wong BI. Normothermic versus hypothermic cardiopulmonary bypass· central nervous system outcomes *J Cardiothorac Vasc Anesth* 1996; **10**: 45–52

86 McLean RF, Wong BI, Naylor CD, Snow WG, Harrington EM, Gawel M. Cardiopulmonary bypass, temperature, and central nervous system dysfunction. *Circulation* 1994, **90**: II250–5

87 Menasche P, Pasquier C, Bellucci S, Lorente P, Jaillon P, Piwnica A Deferoxamine reduces neutrophil-mediated free radical production during cardiopulmonary bypass in man *J Thorac Cardiovasc Surg* 1988, **96**: 582–9

88 Metz S. Pro: glucose priming solutions should be used for cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1995; **9**· 603–4

89 Metz S, Keats AS Benefits of a glucose-containing priming solution for cardiopulmonary bypass *Anesth Analg* 1991; **72**. 428–34

90 Metz S, Slogoff S. Thiopental sodium by single bolus dose compared to infusion for cerebral protection during cardiopulmonary bypass. *J Clin Anesth* 1990; **2**. 226–31

91 Mills SA. Cerebral injury and cardiac operations *Ann Thorac Surg* 1993; **56**: S86–91

92 Moody DM, Bell MA, Challa VR, Johnston WE, Prough DS Brain microemboli during cardiac surgery or aortography *Ann Neurol* 1990; **28**: 477–86

93 Mora CT, Henson MB, Weintraub WS, *et al.* The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization. *J Thorac Cardiovasc Surg* 1996; **112**. 514–22

94 Murkin JM. Anesthesia, the brain, and cardiopulmonary bypass. *Ann Thorac Surg* 1993, **56**: 1461–3

95 Murkin JM, Farrar JK, Tweed WA, McKenzie FN, Guiraudon G Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $PaCO_2$. *Anesth Analg* 1987; **66**: 825–32

96 Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J Thorac Cardiovasc Surg* 1995; **110**: 349–62

97 Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery *Ann Thorac Surg* 1995; **59** 1289–95

98 Murkin JM, Stump DA, Blumenthal JA, McKhann G. Defining dysfunction: group means versus incidence analysis—a statement of consensus. *Ann Thorac Surg* 1997; **64** 904–5

99 Murphy PM Pro: intraoperative transesophageal echocardiography is a cost-effective strategy for cardiac surgical procedures. *J Cardiothorac Vasc Anesth* 1997; **11**: 246–9

100 Mutch WA, Ryner LN, Kozlowski P, *et al.* Cerebral hypoxia during cardiopulmonary bypass: a magnetic resonance imaging study. *Ann Thorac Surg* 1997, **64**: 695–701

101 Nakai H, Yamamoto YL, Diksic M, Worsley KJ, Takara E. Triple-tracer autoradiography demonstrates effects of hyperglycemia on cerebral blood flow, pH, and glucose utilization in cerebral ischemia of rats. *Stroke* 1988; **19**: 764–72

102 Nakashima K, Todd MM. Effects of hypothermia on the rate of excitatory amino acid release after ischemic depolarization. *Stroke* 1996; **27**: 913–18

103 Nathan HJ, Munson J, Wells G, Mundi C, Balaa F, Wynands JE. The management of temperature during cardiopulmonary bypass: effect on neuropsychological outcome. *J Card Surg* 1995; **10**: 481–7

104 Nevin M, Colchester AC, Adams S, Pepper JR. Evidence for involvement of hypocapnia and hypoperfusion in aetiology of neurological deficit after cardiopulmonary bypass. *Lancet* 1987; **ii**: 1493–5

105 Newman MF, Croughwell ND, Blumenthal JA, *et al.* Predictors of cognitive decline after cardiac surgery. *Ann Thorac Surg* 1995; **59**: 1326–30

106 Newman MF, Croughwell ND, Blumenthal JA, *et al.* Effect of aging on cerebral autoregulation during cardiopulmonary bypass. Association with postoperative cognitive dysfunction. *Circulation* 1994; **90**: II243–9

107 Newman MF, Croughwell ND, White WD, *et al.* Effect of perfusion pressure on cerebral blood flow during normothermic cardiopulmonary bypass. *Circulation* 1996; **94**: II353–7

108 Newman MF, Kramer D, Croughwell ND, et *al.* Differential age effects of mean arterial pressure and rewarming on cognitive dysfunction after cardiac surgery. *Anesth Analg* 1995; **81**: 236–42

109 Newman MF, Murkin JM, Roach G, et *al.* Cerebral physiologic effects of burst suppression doses of propofol during nonpulsatile cardiopulmonary bypass. CNS Subgroup of McSPI. *Anesth Analg* 1995; **81**: 452–7

110 Newman MF, Reves JG. Feeling the heat. *J Cardiothorac Vasc Anesth* 1997; **11**: 687–8

111 Newman MF, Wolman R, Kanchuger M, *et al.* Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Circulation* 1996; **94**: II74–80

112 Newman S. The incidence and nature of neuropsychological morbidity following cardiac surgery. *Perfusion* 1989; **4**: 93–100

113 Newman SP. Analysis and interpretation of neuropsychologic tests in cardiac surgery. *Ann Thorac Surg* 1995; **59**: 1351–5

114 Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology* 1986; **64**: 165–70

115 Pascoe EA, Hudson RJ, Anderson BA, *et al.* High-dose thiopentone for open-chamber cardiac surgery: a retrospective review. *Can J Anaesth* 1996; **43**: 575–9

116 Pickard JD, Murray GD, Illingworth R, *et al.* Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ* 1989; **298**: 636–42

117 Prough DS, Rogers AT, Stump DA, *et al.* Cerebral blood flow decreases with time whereas cerebral oxygen consumption remains stable during hypothermic cardiopulmonary bypass in humans. *Anesth Analg* 1991; **72**: 161–8

118 Pugsley W. The use of Doppler ultrasound in the assessment of microemboli during cardiac surgery. *Perfusion* 1989; **4**: 115–22

119 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994; **25**: 1393–9

120 Regragui I, Birdi I, Izzat MB, *et al.* The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: a prospective randomized trial. *J Thorac Cardiovasc Surg* 1996; **112**: 1036–45

121 Reves JG, White WD, Amory DW. Improvement of outcomes after coronary artery bypass. *J Thorac Cardiovasc Surg* 1996; **113**: 1118–20

122 Roach GW. Pro: prevention of neurologic dysfunction associated with cardiac surgery requires pharmacologic brain protection. *J Cardiothorac Vasc Anesth* 1997; **11**: 793–5

123 Roach GW, Kanchuger M, Mora Mangano C, *et al.* Adverse cerebral outcomes after coronary artery bypass surgery. *New Engl J Med* 1996; **335**: 1857–63

124 Rogers A. Con: preventing stroke after cardiopulmonary bypass does not require pharmacologic neuroprotection. *J Cardiothorac Vasc Anesth* 1997; **11**: 796–800

125 Rogers AT, Prough DS, Roy RC, et *al.* Cerebrovascular and cerebral metabolic effects of alterations in perfusion flow rate during hypothermic cardiopulmonary bypass in man. *J Thorac Cardiovasc Surg* 1992; **103**: 363–8

126 Rogers AT, Prough DS, Stump DA, *et al.* Cerebral blood flow does not change following sodium nitroprusside infusion during hypothermic cardiopulmonary bypass. *Anesth Analg* 1989; **68**: 122–5

127 Rogers AT, Stump DA, Gravlee GP, *et al.* Response to cerebral blood flow to phenylephrine infusion during hypothermic cardiopulmonary bypass. *Anesthesiology* 1988; **69**: 547–51

128 Rorick MB, Furlan AJ. Risk of cardiac surgery in patients with prior stroke. *Neurology* 1990; **40**: 835–7

129 Roses AD, Saunders AM. APOE is a major susceptibility gene for Alzheimer's disease. *Curr Opin Biotechnol* 1994; **5**: 663–7

130 Saunders AM, Hulette O, Welsh-Bohmer KA, et *al.* Specificity, sensitivity, and predictive value of apolipoprotein-E genotyping for sporadic Alzheimer's disease. *Lancet* 1996; **348**: 90–3

131 Savageau JA, Stanton BA, Jenkins CD, Klein MD. Neuropsychological dysfunction following elective cardiac operation. I. Early assessment. *J Thorac Cardiovasc Surg* 1982; **84**: 585–94

132 Schell RM, Kern FH, Greeley WJ, *et al.* Cerebral blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg* 1993; **76**: 849–65

133 Schwartz AE, Sandhu AA, Kaplon RJ, *et al.* Cerebral blood flow is determined by arterial pressure and not cardiopulmonary bypass flow rate. *Ann Thorac Surg* 1995; **60**: 165–9

134 Shaw PJ, Bates D, Cartlidge NE, et *al.* Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987; **18**: 700–7

135 Shaw PJ, Bates D, Cartlidge NEF, Heaviside D, Julian DG, Shaw DA. Early neurological complications of coronary artery bypass surgery. *BMJ* 1985; **291**: 1384–7

136 Sherwin BB. Estrogen and cognitive functioning in women. *Proc Soc Exp Biol Med* 1998; **217**: 17–22

137 Sherwin BB, Tulandi T. 'Add-back' estrogen reverses cognitive deficits induced by a gonadotropin-releasing hormone agonist in women with leiomyomata uteri. *J Clin Endocrinol Metab* 1996; **81**: 2545–9

138 Sieber FE. The neurologic implications of diabetic hyperglycemia during surgical procedures at increased risk for brain ischemia. *J Clin Anesth* 1997; **9**: 334–40

139 Sieber FE, Smith DS, Traystman RJ, Wollman H. Glucose: a reevaluation of its intraoperative use. *Anesthesiology* 1987; **67**: 72–81

140 Sieber FE, Traystman RJ. Special issues: glucose and the brain. *Crit Care Med* 1992; **20**: 104–14

141 Singer CA, Rogers KL, Strickland TM, Dorsa DM. Estrogen protects primary cortical neurons from glutamate toxicity. *Neurosci Lett* 1996; **212**: 13–16

142 Singh AK, Bert AA, Feng WC, Rotenberg FA. Stroke during coronary artery bypass grafting using hypothermic versus normothermic perfusion. *Ann Thorac Surg* 1995; **59**: 84–9

143 Singh AK, Feng WC, Bert AA, Rotenberg FA. Warm body, cold heart: myocardial revascularization in 2383 consecutive patients. *J Cardiovasc Surg* 1993; **34**. 415–21

144 Slogoff S, Reul GJ, Keats AS, *et al.* Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. *Ann Thorac Surg* 1990; **50**: 911–18

145 Smith PK, Muhlbaier LH. Aprotinin: safe and effective only with the full-dose regimen. *Ann Thorac Surg* 1996; **62**: 1575–7

146 Smith PLC, Treasure T, Newman SP, *et al.* Cerebral consequences of cardiopulmonary bypass. *Lancet* 1986; **1**: 823–5

147 Soma Y, Hirotani T, Yozu R, *et al.* A clinical study of cerebral circulation during extracorporeal circulation. *J Thorac Cardiovasc Surg* 1989; **97**: 187–93

148 Sotaniemi KA. Brain damage and neurological outcome after open-heart surgery. *J Neurol Neurosurg Psychiatry* 1980, **43**· 127–35

149 Spencer FC, Rossi NP, Yu S, Koepke JA. The significance of air embolism during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1965, **19**: 615–34

150 Stephan H, Weyland A, Kazmaier S, Henze T, Menck S, Sonntag H. Acid–base management during hypothermic cardiopulmonary bypass does not affect cerebral metabolism but does affect blood flow and neurological outcome. *Br J Anaesth* 1992; **69**: 51–7

151 Stump DA. Selection and clinical significance of neuropsychologic tests. *Ann Thorac Surg* 1995; **59**: 1340–4

152 Stump DA, Rogers AT, Hammon JW, Newman SP. Cerebral emboli and cognitive outcome after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996; **10**: 113–18

153 Taggart DP, Bhattacharya K, Meston N, *et al.* Serum S-100 protein concentration after cardiac surgery: a randomized trial of arterial line filtration. *Eur J Cardiothorac Surg* 1997; **11**: 645–9

154 Taggart DP, Mazel JW, Bhattacharya K, *et al.* Comparison of serum S-100 beta levels during CABG and intracardiac operations. *Ann Thorac Surg* 1997; **63**: 492–6

155 Tardiff BE, Newman MF, Saunders AM, *et al.* Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. *Ann Thorac Surg* 1997; **64**: 715–20

156 Taylor KM, Devlin BJ, Mittra SM, Gillan JG, Brannan JJ, McKenna JM. Assessment of cerebral damage during open-heart surgery A new experimental model. *Scand J Thorac Cardiovasc Surg* 1980; **14**: 197–203

157 The European Study Group on Nimodipine in Severe Head Injury. A multicenter trial of the efficacy of nimodipine on outcome after severe head injury. *J Neurosurg* 1994; **80**: 797–804

158 Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations. *J Thorac Cardiovasc Surg* 1992; **104**· 1510–7

159 Turnipseed WD, Berkoff HA, Belzer FO. Postoperative stroke in cardiac and peripheral vascular disease. *Ann Surg* 1980; **192**: 365–8

160 Ungerleider RM, Kisslo JA, Greeley WJ, Van Trigt P, Sabiston DC jr. Intraoperative prebypass and postbypass epicardial color flow imaging in the repair of atrioventricular septal defects *J Thorac Cardiovasc Surg* 1989; **98**: 90–9

161 Venn GE, Patel RL, Chambers DJ. Cardiopulmonary bypass: perioperative cerebral blood flow and postoperative cognitive deficit. *Ann Thorac Surg* 1995; **59**: 1331–5

162 Venn GE, Sherry K, Klinger L, *et al.* Cerebral blood flow during cardiopulmonary bypass. *Eur J Cardiothorac Surg* 1988, **2** 360–3

163 von Knobelsdorff G, Tonner PH, Hanel F, Bischoff P, Scholz J, Schulte am Esch J. Prolonged rewarming after hypothermic cardiopulmonary bypass does not attenuate reduction of jugular bulb oxygen saturation. *J Cardiothorac Vasc Anesth* 1997; **11**· 689–93

164 Wareing TH, Dávila-Román VG, Barzilia B, Murphy SF, Kouchoukos NT. Management of the severely atherosclerotic ascending aorta during cardiac operations *J Thorac Cardiovasc Surg* 1992; **103**: 453–62

165 Warm Heart Investigators. Randomised trial of normothermic versus hypothermic coronary bypass surgery. *Lancet* 1994; **343**: 559–63

166 Westaby S, Johnsson P, Parry AJ, *et al.* Serum S100 protein a potential marker for cerebral events during cardiopulmonary bypass. *Ann Thorac Surg* 1996; **61**: 88–92

167 Wolbers JG. Brain swelling and coronary artery bypass surgery *Lancet* 1994; **343**: 62

168 Wolman RL, Nussmeier NA, Aggarwal A, *et al.* Cerebral injury after cardiac surgery : identification of a group at extraordinary risk. *Stroke* 1999; **30**: 514–22

169 Yager JY, Asselin J. Effect of mild hypothermia on cerebral energy metabolism during the evolution of hypoxic–ischemic brain damage in the immature rat. *Stroke* 1996; **27**. 919–25

170 Zaidan J, Klochany A, Martin W. Effect of thiopental on neurologic outcome following coronary artery bypass grafting. *Anesthesiology* 1991; **74**: 406–11

British Journal of Anaesthesia 84 (3). 394–5 (2000)

BJA

SHORT COMMUNICATIONS

Residual curarization in the recovery room after vecuronium†

C. Baillard[1]*, G. Gehan[1], J. Reboul-Marty[2], P. Larmignat[1], C. M. Samama[1] and M. Cupa[1]

[1]*Department of Anaesthesiology, University Hospital, Bobigny, France.* [2]*Public Health Unit, School of Medicine, Bobigny, France*

**Corresponding author: Département d'Anesthésie, Hôpital Avicenne, 125 route de Stalingrad, F-93009 Bobigny Cedex, France*

We have investigated residual block after anaesthesia which included the use of the neuromuscular blocking agent vecuronium but no anticholinesterase, in 568 consecutive patients on admission to the recovery room. The ulnar nerve was stimulated submaximally using TOF stimulation (30 mA). Postoperative residual curarization was defined as a TOF ratio <0.7. Of the 568 patients, 239 (42%) had a TOF <0.7 in the recovery room. These patients had received a larger cumulative dose of vecuronium than patients who had full recovery (mean 7.7 (SD 3.6) mg *vs* 6.2 (2.7) mg; $P<0.05$) and a shorter time had elapsed since the last vecuronium dose (117 (70) min *vs* 131 (80) min; $P<0.05$). Of 435 patients whose trachea was extubated, 145 (33%) exhibited inadequate recovery from neuromuscular block. Six of these had one or no response to TOF stimulation and were reintubated. In the remaining 139 patients, neuromuscular block was successfully antagonized. Only 20 patients (3.5%) remembered TOF stimulation when questioned 2 h later in the recovery room, and discomfort associated with it was assessed using a visual analogue scale before discharge. We conclude that it is necessary to antagonize residual block produced by vecuronium.

Br J Anaesth 2000; **84**: 394–5

Keywords: neuromuscular block, vecuronium; neuromuscular block, measurement of response; monitoring, neuromuscular function

Accepted for publication: August 3, 1999

Postoperative residual curarization in conscious patients in the recovery room is a well recognized phenomenon that may increase postoperative morbidity.[1] Prevention of residual curarization depends on clinical assessment, neuromuscular monitoring, use of short- or intermediate-acting neuromuscular blocking drugs, and administration of anticholinesterases in an appropriate dose. Neuromuscular monitoring using train-of-four (TOF) stimulation has been used during operation to identify residual curarization, allowing the dose of anticholinesterase to be adjusted accordingly. Supramaximal stimulation is used during general anaesthesia, but this can be uncomfortable in conscious patients. Submaximal TOF stimulation is reliable and may be more suitable for use in awake patients with suspected residual curarization.[2] Although the incidence of postoperative residual curarization may be lower with intermediate-acting than with long-acting neuromuscular blocking drugs, postoperative residual curarization may still occur.[3 4]

In this prospective study, we have determined the incidence of residual neuromuscular block in the recovery room after the use of vecuronium and evaluated the discomfort associated with submaximal TOF stimulation in awake patients.

Methods and results

After obtaining approval from the Institutional Review Board, we studied prospectively 583 adults given a non-depolarizing neuromuscular blocking drug for a range of surgical procedures (orthopaedic. abdominal, thoracic, vascular) over a 3-month period during 1995. The anaesthetic technique used was similar throughout the study period. No attempt was made to influence the anaesthetic technique and consequently, peroperative neuromuscular monitoring or reversal of curarization were not necessary for inclusion in the study. The choice of drugs used for premedication, anaesthesia and neuromuscular block was at the discretion of the anaesthetist who was unaware that the patient would be assessed in the recovery room.

Most patients were premedicated with hydroxyzine 100 mg orally. After arriving in the operating room, patients were placed on the operating table and kept warm with a blanket. Anaesthesia was induced with propofol 2.5 mg kg^{-1} or etomidate 0.3 mg kg^{-1} and fentanyl 2 μg kg^{-1}. Intubation

---

†This article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

was facilitated in 568 patients by vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained by isoflurane and 60% nitrous oxide in oxygen. Doses of neuromuscular blocking agent required during surgery (intermittent i.v. bolus), adequacy of recovery from neuromuscular block, use of an anticholinesterase and decision to extubate the trachea before arrival in the recovery room were based on clinical criteria only. Ten patients given atracurium and five given rocuronium in the peroperative period were excluded from further study.

Immediately after arrival in the recovery room, the TOF response was measured using an acceleration transducer (TOF-Guard, Organon Teknika, NV), and the TOF ratio was recorded. The ulnar nerve was stimulated submaximally (30 mA) by two skin electrodes placed on the forearm, and the transducer was placed on the volar aspect of the thumb. Postoperative residual curarization was defined as a TOF ratio <0.7, as proposed previously.[3 4] Postoperative residual curarization in a patient whose tracheal tube had been removed was considered to indicate inadequate recovery requiring anticholinesterase therapy. Neostigmine 50 µg kg^{-1} and atropine 15 µg kg^{-1} were given if at least two responses to TOF were detectable, and re-intubation was performed if less than two responses were obtained. Discomfort associated with neuromuscular stimulation was evaluated approximately 2 h after TOF stimulation using a visual analogue scale graded from 0 (no pain) to 10 (intractable pain), before the patient left the recovery room.

Results are expressed as mean (SD). Comparisons between groups were performed using the chi-square and Student's *t* tests. Results were considered statistically significant when $P \leq 0.05$.

Of the 568 patients given vecuronium, neuromuscular monitoring was used in 11 patients in the peroperative period but neuromuscular block was antagonized in the operating room in only one patient.

Inadequate recovery from neuromuscular block in the recovery room was found in 239 (42%) patients. These patients were older than patients with adequate recovery (mean 50 (range 18–83) yr *vs* 45 (18–85) yr; $P<0.05$), had received a larger cumulative dose of vecuronium (mean 7.7 (SD 3.6) mg *vs* 6.2 (2.7) mg; $P<0.05$) and a shorter time had elapsed since the last dose of vecuronium (117 (70) min *vs* 131 (80) min; $P<0.05$) (Table 1).

In 435 patients the trachea was extubated in the operating room; 145 of these (33%) had a TOF ratio <0.7 on arrival in the recovery room. Six had one or no response to submaximal TOF stimulation and the trachea was reintubated. In the remaining 139 patients, with at least two responses to TOF stimulation, neuromuscular block was antagonized successfully with neostigmine 50 µg kg^{-1}.

Only 20 patients (3.5%) remembered TOF stimulation before discharge from the recovery room, and only one had a visual analogue scale score >3.

Table 1 Patient and clinical characteristics of patients with adequate *vs* inadequate recovery from neuromuscular block produced by vecuronium in the recovery room (mean (SD or range), median [range] or number). *$P<0.05$

	Adequate recovery	**Inadequate recovery**
n	329	239
ASA score	II [I–IV]	II [I–IV]
Sex (M/F)	190/139	141/98
Age (yr)	45 (18–85)	50 (18–83)*
Weight (kg)	69 (13)	68 (13)
Extubated/intubated before admission to the recovery room	290/39	145/94
Body core temperature in the recovery room (°C)	35.8 (0.4)	35.7 (0.3)
Time of isoflurane exposure (min)	101 (83)	95 (79)
Vecuronium total dose (mg)	6.2 (2.7)	7.7 (3.6)*
Time from last injection to TOF recording in recovery room (min)	131 (80) [20–360]	117 (70) [20–360]*

Comment

Our study highlights the need to antagonize routinely vecuronium-induced neuromuscular block even though it is considered to be an intermediate-acting agent. It also emphasizes the need to monitor neuromuscular block in the peroperative period if there is a need to avoid the use of an anticholinesterase at the end of surgery. A TOF ratio of 0.7 was, until recently, the threshold above which recovery was thought to be adequate.[3 4] But it is now considered that a TOF ratio of 0.9 is necessary to avoid the risk of passive regurgitation and aspiration.[5 6] Thus residual curarization will be present more frequently than is supposed.

The results of this study suggest that as with mivacurium,[6] anaesthetists should use an anticholinesterase after vecuronium. We have modified our clinical practice as a result of this study.

References

1 Berg H, Roed J, Viby-Mogensen J, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41**: 1095–103

2 Brull SJ, Ehrenwerth J, Silverman DG. Stimulation with submaximal current for train-of-four monitoring. *Anesthesiology* 1990; **72**: 629–32

3 Fawcett WJ, Dash A, Francis GA, Liban JB, Cashman JN. Recovery from neuromuscular blockade: residual curarisation following atracurium or vecuronium by bolus dosing or infusions. *Acta Anaesthesiol Scand* 1995; **39**: 288–93

4 Bevan DR, Kahwaji R, Ansermino LM, *et al.* Residual block after mivacurium with or without edrophonium reversal in adults and children. *Anesthesiology* 1996; **84**: 362–7

5 Eriksson LI, Sundman E, Olson R, *et al.* Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans. *Anesthesiology* 1997; **87**: 1035–43

6 Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology* 1997; **86**: 765–71

British Journal of Anaesthesia 84 (3): 396–8 (2000)

Effect of intraoperative angiotensin-converting enzyme inhibition by quinaprilat on hypertension after coronary artery surgery

M. Müller[1]*, E. Schindler[1], M. Kwapisz[1], S. Klemm[1], H. Akintürk[2], M. Heidt[2] and G. Hempelmann[1]

[1]Department of Anaesthesiology and Intensive Care Medicine and [2]Department of Cardiovascular Surgery, Justus-Liebig-University Giessen, Rudolf-Buchheim-Str. 7, D-35392 Giessen, Germany

**Corresponding author*

Activation of the renin–angiotensin system during cardiopulmonary bypass (CPB) may be involved in early postoperative hypertension after coronary artery bypass grafting (CABG). As hypertensive episodes may be deleterious in the immediate postoperative period, we have assessed the effects of prophylactic treatment with the angiotensin-converting enzyme inhibitor quinaprilat in an open study. During steady state CPB, patients received quinaprilat 0.02 mg kg^{-1} (group A, $n=10$), quinaprilat 0.04 mg kg^{-1} (group B, $n=10$) or saline solution (group C, $n=10$) as an i.v. bolus dose. Sodium nitroprusside (SNP) was given after operation when systolic arterial pressure was >150 mm Hg. Requirements for SNP 1 h after arrival in the ICU were significantly less in groups A (two of 10) and B (two of 10) than in group C (eight of 10). Also, patients in group C had a greater systolic arterial pressure compared with groups A and B. There were no significant differences between groups in diastolic arterial pressure, heart rate, cardiac index or cardiac filling pressures. We conclude that quinaprilat can be used during CABG to reduce the incidence of postoperative hypertension. Further studies of the efficacy and safety of this technique are necessary.

Br J Anaesth 2000; **84**: 396–8

Keywords: heart, quinaprilat; pharmacology, quinaprilat; complications, hypertension; surgery cardiovascular

Accepted for publication: October 15, 1999

Postoperative hypertension is a common problem in patients undergoing coronary artery bypass grafting (CABG).[1] The consequences of perioperative hypertension may be deleterious and include an increase in myocardial workload and myocardial oxygen consumption in addition to bleeding from vascular suture lines and cerebrovascular haemorrhage. It has been shown that an increase in systemic vascular resistance is a major determinant of increased arterial pressure. In addition to neurogenic reflexes, humoral factors such as epinephrine, norepinephrine, renin and angiotensin have been implicated in the pathophysiology of vasoconstriction.[2] Little information is available on the prophylactic use of angiotensin-converting enzyme (ACE) inhibitors to prevent hypertension after cardiac surgery.

Quinaprilat is the active metabolite of the non-sulphydryl ACE inhibitor quinapril. Its onset time after i.v. administration is within 15 min and its duration of action is at least 12 h.[3] No data are available on the effects of quinaprilat as prophylactic treatment of postoperative hypertension. The aim of this open study was to evaluate the effects of intraoperative pretreatment with quinaprilat i.v. on the incidence of hypertension after cardiac surgery.

Methods and results

After obtaining approval from the Local Ethics Committee and informed consent, we studied 30 patients undergoing elective CABG. Patients with pre-existing cardiac failure (ejection fraction <50%, as estimated by ventriculography), renal insufficiency (serum creatinine >2.0 mmol $litre^{-1}$) or impaired liver function (GOT >30 u. $litre^{-1}$, GPT >30 u. $litre^{-1}$), and those receiving ACE inhibitors or who suffered previous unacceptable side effects from ACE inhibitors were excluded. Using a randomized sequence, patients were allocated prospectively to group A (quinaprilat 0.02 mg kg^{-1}, $n=10$), group B (quinaprilat 0.04 mg kg^{-1}, $n=10$) or group C (control, $n=10$). Preoperative drug treatment included nitrates (group A, $n=8$; group B, $n=9$; group C, $n=3$), beta-adrenergic blocking drugs (group A, $n=6$; group B, $n=6$; group C, $n=7$) and calcium channel blockers (group A, $n=3$; group B, $n=4$; group C, $n=3$). These were continued until the day of surgery.

On the morning of surgery, patients received flunitrazepam 2 mg and morphine 30 mg for oral premedication, approximately 1 h before anaesthesia. Anaesthesia was

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

induced with sufentanil 0.2–0.3 μg kg^{-1} i.v., midazolam 0.05–0.1 mg kg^{-1} i.v. and pancuronium 0.1 mg kg^{-1} i.v. For maintenance of anaesthesia, sufentanil 25 μg every 30 min and midazolam 5 mg every 45 min were given. Pancuronium and further doses of sufentanil and midazolam were given as required. Total doses of anaesthetic agents were similar for all patients (sufentanil: mean 4.8 (SD 1.4) μg kg^{-1} in group A, 4.2 (1.0) μg kg^{-1} in group B and 4.2 (1.0) μg kg^{-1} in group C; midazolam: 0.6 (0.1) mg kg^{-1} in group A, 0.5 (0.1) mg kg^{-1} in group B and 0.5 (0.1) mg kg^{-1} in group C). Invasive haemodynamic monitoring using arterial and pulmonary artery catheters was performed. Before cardiopulmonary bypass (CPB), anaesthesia was supplemented with nitrous oxide.

CPB was performed during moderate hypothermia (rectal temperature ≥33°C) using non-pulsatile perfusion (2.4 litre min^{-1} m^{-2}) with membrane oxygenators (Sorin 41; Sorin, Torino, Italy). Priming of the extracorporeal circuit consisted of Ringer's solution 2000 ml and 5% albumin solution 250 ml and electrolytes. Histidine tryptophane ketoglutarate (HTK) solution was used for cardioplegic arrest. A monoatrial cannulation technique and 'partial' CPB were used. In all patients, rewarming began using the integral heat exchanger of the oxygenator and a warming mattress when the final distal anastomosis was started. Rewarming was adjusted to reach 37°C before weaning from CPB was started. After CPB, blood remaining in the extracorporeal circuit was salvaged using a haemofiltration technique and autologous blood was retransfused. The therapeutic management of patients during anaesthesia and in the ICU followed the standard procedures of our institution and was performed by physicians who were not involved in the study. Postoperative systolic arterial pressure (SAP) greater than 150 mm Hg for more than 5 min, despite adequate analgesia and sedation in the intubated and normoventilated patient, was defined as an indication for sodium nitroprusside (SNP).

Haemodynamic variables, including cardiac output measured by thermodilution (mean of three measurements), were recorded. The need for inotropic, vasoconstrictor or vasodilator drugs after operation was noted. Baseline values were measured during steady state anaesthesia before surgery (T0). During steady state CPB (approximately 20 min after the start of CPB, after haemoconcentration and stabilization of temperature), quinaprilat (groups A and B) or saline solution (group C) was given as an i.v. bolus. Measurements were repeated 5 min after weaning off CPB (T1), at the end of surgery (T2) and 60 min after arrival in the ICU (T3). During CPB, norepinephrine was given to maintain mean arterial pressure (MAP) >50 mm Hg. When MAP was >100 mm Hg, sufentanil 0.2 μg kg^{-1} and midazolam 0.1 mg kg^{-1} were given followed by a vasodilator when necessary. All patients who received norepinephrine (n=0) after application of the test drugs or those that required another vasodilator (group B, n=1; group C, n=1) were excluded.

Table 1 Haemodynamic data (mean (SD)) in the three groups. HR=Heart rate, CI=cardiac index, SAP=systolic arterial pressure, DAP=diastolic arterial pressure, CVP=central venous pressure, and PCWP=pulmonary capillary wedge pressure. T0=Baseline, T1=after CPB, T2=end of surgery, and T3=1 h after arrival in the ICU *$P<0.05$ compared with baseline (T0) values, †$P<0.05$ *vs* placebo

	T0	T1	T2	T3
HR (beat min^{-1})				
Group A	68 (15)	91 (18)*	95 (7)*	97 (20)*
Group B	70 (9)	90 (11)*	96 (10)*	97 (12)*
Group C	60 (12)	90 (15)*	93 (14)*	91 (15)*
CI (litre min^{-1} m^{-2})				
Group A	2.21 (0.5)	3.53 (0.7)*	2.90 (0.6)	2.88 (0.8)
Group B	2.42 (0.4)	3.44 (1)*	2.87 (0.6)	3.1 (1)
Group C	2.13 (0.5)	3.02 (0.5)*	2.47 (0.6)	2.51 (0.6)
SAP (mm Hg)				
Group A	115 (21)	111 (13)	111 (11)	143 (24)*†
Group B	112 (21)	112 (16)	118 (12)	141 (28)*†
Group C	126 (19)	114 (22)	123 (17)	171 (32)*
DAP (mm Hg)				
Group A	55 (10)	59 (10)	62 (8)	76 (18)*
Group B	59 (11)	56 (7)	62 (11)	72 (16)*
Group C	60 (12)	56 (10)	61 (11)	85 (20)*
CVP (mm Hg)				
Group A	6 (3)	6 (3)	6 (3)	10 (4)
Group B	7 (4)	6 (3)	8 (4)	10 (3)
Group C	6 (4)	5 (3)	6 (3)	7 (3)
PCWP (mm Hg)				
Group A	11 (4)	11 (3)	10 (4)	13 (4)
Group B	11 (5)	9 (3)	11 (7)	13 (3)
Group C	10 (4)	9 (6)	9 (3)	11 (5)

For statistical analysis, the SPSS 7.5 for Windows 95 NT computer package was used. For a power of 80%, 10 patients in each group were required to demonstrate 50% reduction in the incidence of postoperative hypertension. Data are expressed as mean (SD). Baseline data (T0) and consecutive data (T1, T2, T3) for each group of patients were compared using the t test for dependent samples. To determine differences between groups, the t test for independent samples was used. For categorical data, Fisher's exact test was used. $P<0.05$ was considered significant.

Patient characteristics and details of the surgical procedures did not differ between groups. Haemodynamic data are presented in Table 1. In all three groups, SAP and diastolic arterial pressure (DAP) were significantly higher at T3 compared with baseline. However, SAP at T3 was significantly lower in both groups who received quinaprilat compared with controls. At T3, eight patients in the control group required infusion of SNP to compensate for acute postoperative hypertension compared with two patients in group A and two in group B. There was no difference between groups in heart rate, cardiac index, central venous pressure or pulmonary capillary wedge pressure. No patient received inotropics or vasoconstrictors during or after weaning from CPB.

Comment

Although plasma angiotensin II concentrations were not measured in this study, it has been shown previously that activation of the renin–angiotensin system with increased concentrations of angiotensin II occurs during CPB and may be involved in hypertension after coronary bypass.[2] Our data may indicate that block of the renin–angiotensin system with quinaprilat during coronary artery bypass surgery can be used to prevent postoperative hypertension. In contrast with our findings, Colson and colleagues reported that preoperative block of the renin–angiotensin system using an oral ACE inhibitor failed to prevent hypertension after coronary artery surgery.[4] However, this group used captopril, an ACE inhibitor with a lower inhibitory potency and a shorter half-life than quinaprilat. Boldt and colleagues reported that i.v. administration of the ACE inhibitor enalaprilat was effective in reducing arterial pressure in hypertensive patients during CABG.[5] Unfortunately, no data concerning postoperative haemodynamics were presented. We found no difference between the intervention and control groups in the use of inotropes and vasoconstrictors during and after weaning off CPB. However, Tuman and colleagues reported that preoperative use of oral ACE inhibitors was associated with an increase in vasoconstrictor requirements after CPB.[6]

Data collection in our study was prospective and, although the study was not blinded, it was designed to identify variations in a uniform group of patients undergoing a standardized procedure during a short observation period. Management of patients was consistent between the control and quinaprilat groups. The only difference was the introduction of quinaprilat. Our data suggest that quinaprilat can be used during CABG to reduce the incidence of postoperative hypertension. Further studies are necessary to confirm these results and to comment on the safety of this technique.

References

1 Leslie JB. Incidence and aetiology of perioperative hypertension. *Acta Anaesthesiol Scand Suppl.* 1993; **99**: 5–9

2 Taylor KM, Bain WH, Morton JJ. The role of angiotensin II in the development of peripheral vasoconstriction during open-heart surgery. *Am Heart J* 1980; **100**: 935–7

3 Breslin E, Posvar E, Neub M, Trenk D, Jahnchen E. A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. *J Clin Pharmacol* 1996; **36**: 414–21

4 Colson P, Grolleau D, Chaptal PA, Ribstein J, Mimran A, Roquefeuil B. Effect of preoperative renin–angiotensin system blockade on hypertension following coronary surgery. *Chest* 1988; **93**: 1156–8

5 Boldt J, Schindler E, Wollbruck M, Gorlach G, Hempelmann G. Cardiorespiratory response of intravenous angiotensin-converting enzyme inhibitor enalaprilat in hypertensive cardiac surgery patients. *J Cardiothorac Vasc Anesth* 1994; **37**: 341–6

6 Tuman KJ, McCarthy RJ, O'Connor CJ, Holm WE, Ivankovich AD. Angiotensin-converting enzyme inhibitors increase vasoconstrictor requirements after cardiopulmonary bypass. *Anesth Analg* 1995; **80**: 473–9

British Journal of Anaesthesia 84 (3): 399–400 (2000)

Warm air sensation for assessment of block after spinal anaesthesia

J. Shah[1], B. T. Ayorinde[1], D. J. Rowbotham[2] and D. J. Buggy[1*]

[1]University Department of Anaesthesia, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK. [2]University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK

**Corresponding author*

We have evaluated a new method of assessing dermatomal sensory levels after regional anaesthesia based on warm sensation. Sensory levels were assessed in 30 patients after spinal anaesthesia using a respiratory gas humidifier, adapted to deliver a constant flow of warm air at 40±0.2°C. This was compared with the cold sensation from ethyl chloride spray. The frequency distribution of the dermatomal differences showed 96.6% of the comparisons were between +1 and −1 dermatomes. The median difference in dermatomal levels between the two methods of assessment was 0 (interquartile range 0–1) (P=0.65). We conclude that the warm air method compares favourably with ethyl chloride spray and both can be used interchangeably.

Br J Anaesth 2000; **84**: 399–400

Keywords: anaesthetic techniques, subarachnoid; neuromuscular block; monitoring, neuromuscular function

Accepted for publication: October 14, 1999

Assessment of dermatomal sensory level is necessary to monitor the efficacy and safety of spinal anaesthesia. The standard methods for testing sensory block in the clinical setting are ethyl chloride spray and pinprick, but these are associated, respectively, with pollution and expense, and discomfort and infection. Other methods that have been described for assessment of sensory block include the skin vasomotor reflex, a pressure palpator, a pricking pain roller, self-assessment using light touch and a gas jet method.[1–5] As with cold sensation perceived from ethyl chloride spray, warm sensation is perceived by heat receptors located in the skin. Temperatures from 37 to 44°C are perceived as comfortably warm, with higher values being perceived as painful.[6]

In this study, our objective was to compare the results of assessing dermatomal sensory levels using ethyl chloride spray with those obtained using warm air sensation, delivered by a specially adapted respiratory gas humidifier system.

Methods and results

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 30 patients (mean age 30.5 (range 18–38) yr) undergoing elective Caesarean section under regional anaesthesia. All patients had a combined spinal–epidural (CSE) anaesthetic technique. Subarachnoid block was established with a solution of 2.2 ml of 0.5% hyperbaric bupivacaine and fentanyl 20 µg (0.4 ml). The epidural component of the CSE was not used until the study was completed as all patients had excellent surgical anaesthesia with the spinal component of the CSE and because it is our practice to reserve the epidural route for postoperative analgesia when the spinal has regressed.

In the recovery room at the end of surgery, sensory level was assessed independently by two anaesthetists, one using ethyl chloride spray and the other using the warm air sensation method, at the mid-clavicular line. The sequence of testing was allocated randomly and the second anaesthetist who was not present during the first anaesthetist's assessment conducted his tests immediately afterwards and recorded his findings separately. Testing was performed in a caudal to cephalic (numb to normal) direction and recorded on a standard dermatome chart.

A respiratory gas humidifier (MR-730, Fischer and Paykel) was adapted to produce a warm air outflow at 40±0.2°C. The humidifier was calibrated using set point precision resistors and contained two safety cut-out thermostats to prevent burns to the patient's skin. Wall oxygen, flowing at 10 litre min^{-1}, was connected to the heating chamber inlet. The outflow tubing (5 mm in diameter) was held 1 cm from the patient's skin, giving a pleasantly warm sensation. A thermistor at the patient end of the tubing

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

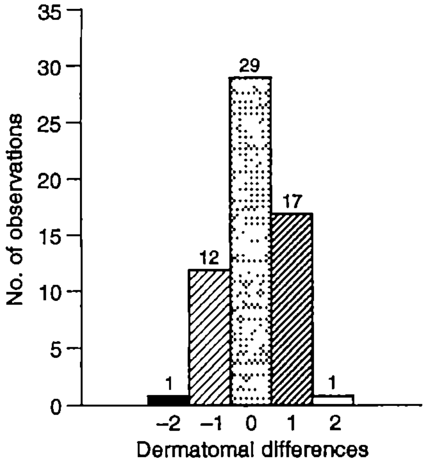


Fig 1 Frequency distribution of dermatomal differences for the two methods of assessment after bilateral testing on 30 patients in a caudal to cephalic direction.

confirmed the outflow gas temperature. Before assessment of sensory levels, both warm and cold sensations were experienced by the patient on normal, unanaesthetized skin on the forearm. All patients reported a sensation of warmth, rather than a flow of air, when tested with the warm air device. The sensory level recorded was that at which the patient felt the sensation was the same as on the unanaesthetized forearm. The dermatomal difference between the two methods was defined as warm air dermatomal level minus ethyl chloride dermatomal level. The differences in dermatomal sensory levels were compared using the Wilcoxon signed ranks test for paired differences.

Bilateral testing on 30 patients in a caudal to cephalic direction provided 60 comparisons. The frequency distribution of the dermatomal differences (Fig. 1) showed 96.6% of the comparisons lay between +1 and –1 dermatomes. The dermatomal differences were not distributed normally (Komolgorov–Smirnov test, P=0.001). The median difference in dermatomal levels for the two methods of assessment was 0 (interquartile range 0–1) (P=0.65).

Comment

Our data showed that warm air sensation compared favourably with ethyl chloride spray for assessment of dermatomal sensory level. Thermal gradations are discriminated by at least three types of receptors: cold, heat and pain.[6] Their presence explains the ability to perceive different gradations of cold and heat ranging from 'freezing cold' to 'burning hot'. Both cold and heat receptors are located under the skin at discrete points, with 3–10 times as many cold receptors as heat receptors.[6] This discrepancy in receptor numbers did not seem to affect the ability of patients to localize the warm stimulus in this study. Pain receptors start to respond to a heat stimulus at about 45°C. We chose a temperature of 40°C to prevent confusion caused by stimulation of nociceptors.

Recently it was found that a gas jet delivered at room temperature compared favourably with ethyl chloride and pinprick, but not as well with light touch sensation.[5] Another study found that self-assessment of light touch was not as reliable a method of assessing sensory levels during labour as ethyl chloride spray.[4] The findings of these two studies and ours may be explained by the fact that pain, heat and cold sensations are transmitted via the anterolateral sensory pathways, while light touch is transmitted via the dorsal columns of the spinal cord. The non-parametric difference in dermatomal sensory level observed in our study would not have had any significant bearing on the outcome.

We have shown that assessment of sensory levels based on warm sensation provided a simple, non-invasive and reliable alternative to ethyl chloride spray, without the disadvantages of pollution. We are in the process of designing a small, portable instrument which will provide a flow of warm air at 40–43°C.

Acknowledgements

We thank Fischer and Paykel for donation of the humidifier. We also thank Kevin Reader, Department of Medical Physics, Leicester General Hospital, for technical assistance.

References

1 Ikuta Y, Shimoda O, Ushijima K, Terasaki H. Skin vasomotor reflex as an objective indicator to assess level of regional anesthesia. *Anesth Analg* 1998; **86**: 336–40

2 Fassoulaki A, Sarantopoulos C, Zotou M, Karabinis G. Assessment of the level of sensory block after subarachnoid anesthesia using a pressure palpator. *Anesth Analg* 1999; **88**: 398–401

3 Shah J, Owen-Smith O, Coley S, Jeyapalan I, Atcheson R, May A. The pricking pain roller for assessment of sensory block after spinal anaesthesia. *Int Monit Reg Anaesth* 1998; **10**: 16

4 Bourne TM, Campbell F, Mushambi MC, May AE. Patients' assessment of sensory levels during extradural anesthesia in labor. *Int J Obstet Anesth* 1997; **6**: 239–41

5 Hughes JC, Harmer M. A new gas jet method for the assessment of sensory block after spinal anaesthesia. *Anaesthesia* 1998; **53**: 197–200

6 Guyton AC, Hall JE. Textbook of *Medical Physiology*, 9th Edn. Philadelphia: WB Saunders, 1996; 595–620

British Journal of Anaesthesia **84** (3): 401–2 (2000)

Caudal clonidine for postoperative analgesia in adults

A. C. Van Elstraete[1*], F. Pastureau[1], T. Lebrun[1] and H. Mehdaoui[2]

[1]*Department of Anaesthesiology, Saint-Paul Medical Center, Fort-de-France, Martinique, France.*
[2]*Intensive Care Unit, University Hospital, Fort-de-France, Martinique, France*
**Corresponding author: Département d'Anesthésiologie, Centre Médico-Chirurgical Saint-Paul, Clairière, 97200 Fort-de-France, Martinique, France*

We have assessed the analgesic efficacy and side effects of caudally administered clonidine in a prospective, randomized, double-blind, placebo-controlled study. We studied 64 adult patients undergoing elective haemorrhoidectomy. Caudal block was performed in all patients using a mixture of 0.5% bupivacaine 35 mg with 2% lidocaine 140 mg and epinephrine 5 µg ml^{-1}. Patients were allocated randomly to one of two groups. Clonidine 75 µg was added in group C and saline 1 ml in group S. Median time to first analgesic requirements was significantly longer in group C (mean 729 (SD 120) min) than in group S (276 (131) min) (P=0.01). Bradycardia occurred in seven patients in group C but did not affect mean arterial pressure.

Br J Anaesth 2000; **84**: 401–2

Keywords: analgesia, postoperative; anaesthetic techniques, regional, caudal; sympathetic nervous system, clonidine

Accepted for publication: October 4, 1999

Clonidine prolongs analgesia when added to local anaesthetics in epidural anaesthesia, subarachnoid anaesthesia and plexus anaesthesia in adults.[1] However, its use is associated with side effects including hypotension, bradycardia and sedation.[1] Addition of clonidine to local anaesthetics significantly prolongs the duration of surgical analgesia of caudal block in children.[2–4] Caudal anaesthesia is not as popular in adults as it is in children but can be used for sacro-perineal surgery. Therefore, in this prospective, double-blind, randomized, placebo-controlled study, we assessed the efficacy of caudally administered clonidine on duration of postoperative analgesia and side effects in adult patients when added to local anaesthetics.

Methods and results

After obtaining approval from the Institutional Review Board and informed consent, we studied 64 ASA I or II patients undergoing elective haemorrhoidectomy performed by the same surgeon. Exclusion criteria included contraindications to caudal block, and chronic use of opioids, calcium channel blockers, clonidine and related compounds. All patients received oral premedication with hydroxyzine 1 mg kg^{-1}, 1 h before surgery.

Standard intraoperative monitoring was used. All patients received a caudal injection of a mixture containing 0.5% isobaric bupivacaine 35 mg with 2% isobaric lidocaine 140 mg and epinephrine 5 mg ml^{-1}. Patients were allocated to one of two groups using a table of random numbers. Clonidine 75 µg (group C) or saline 1 ml (group S) was added to the mixture. Patients were unaware of their treatment group. No infusion was given throughout the study.

Mean systemic arterial pressure (MAP) and heart rate (HR) were measured using a non-invasive automated oscillometric device before operation, every 5 min during operation and 15, 30, 60, 120 and 180 min after operation. Intra- and postoperative follow-up was performed by a blinded observer. Duration of analgesia was defined as the time from caudal injection to the first request for supplementary analgesics. For patients not requiring analgesics within the 48-h observation period, duration of analgesia was defined as 2880 min. Degree of motor block was evaluated using the Bromage scale. Sedation score was assessed on a four-point categorical scale as: 0=alert, aware; 1=drowsy, not sleeping; 2=asleep, arousable by verbal contact; and 3=asleep, not arousable by verbal contact. Time to first micturition, or need for bladder catheterization were recorded.

Bradycardia, defined as a 20% decrease in HR compared with preoperative values, was treated with atropine 0.5 mg i.v. Hypotension, defined as a 20% decrease in MAP compared with preoperative values, was treated with ephedrine 5 mg i.v.

Patient data were analysed using two-way analysis of variance (ANOVA) and the unpaired Student's t test. Time to the first request for supplementary analgesics, time to first micturition and time to first spontaneous standing were compared using ANOVA followed by the Neuman–Keuls test if differences between groups were found. Non-paramet-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

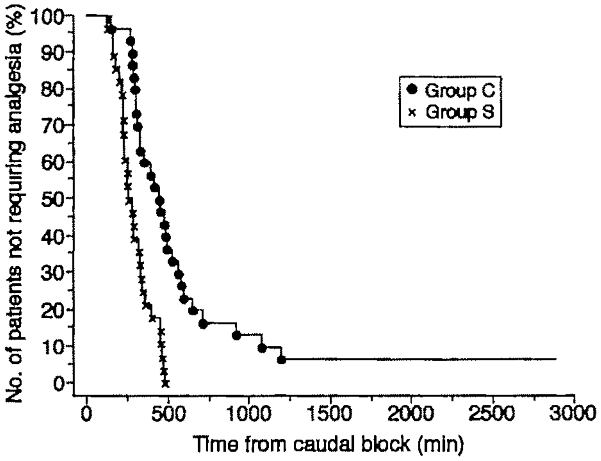


Fig 1 Kaplan–Meier survival curve describing the effect of additives to local anaesthetics on duration of analgesia. Time from caudal anaesthesia to first request for analgesics was significantly longer in group C compared with group S (P=0.01).

ric data were analysed using two-way ANOVA for repeated measures and the Mann–Whitney U test. Nominal data were analysed using the chi-square test. The efficacy of the technique was analysed by survival curves using the Kaplan–Meier method, followed by the log rank test. Results are expressed as mean (SD). $P<0.05$ was considered significant. All analyses were performed using the statistical package Statview (Statview for Windows and Macintosh, version 5, SAS Institute Inc., Cary, NC) on Windows 98.

There were 34 patients in group C and 30 in group S. Six patients did not complete the study because of failure of the caudal block (four in group C and two in group S). No intraoperative analgesic supplements were needed. The groups were similar in age (44.7 (range 31–65) *vs* 49.1 (23–92) yr), weight (72.5 (2.8) *vs* 70.3 (3.1) kg), height 171.4 (1.8) *vs* 167.3 (1.9) cm), male/female ratio (14/16 *vs* 15/13) and duration of surgery (30.1 (0.9) *vs* 29.8 (0.9) min). Median time to first analgesia was significantly longer in group C (729 (120) min) than in group S (276 (131) min) (P=0.01) (Fig. 1). Two patients in group C , compared with none in group S, required no postoperative analgesia (ns).

Ephedrine was not needed in either group. Seven patients in group C and none in group S required atropine (P= 0.006). Four patients in group C compared with one in group S had a sedation score of 1 lasting 30–45 min (ns). Time to first supported standing (148 (27) min in group C and 141 (26) min in group S) (ns) and spontaneous voiding (first micturition 403 (33) min in group C and 406 (36) min in group S) were similar in both groups. No patient required bladder catheterization.

Comment

Our results demonstrated that clonidine 75 µg added to caudally administered local anaesthetics significantly increased the duration of postoperative analgesia in adult patients undergoing elective haemorrhoidectomy. Our findings are consistent with those reported in children[2–4] and adults after epidural clonidine added to local anaesthetics.[1]

Neuraxial administration of clonidine directly inhibits sympathetic preganglionic neurones in the spinal cord with resulting hypotension and bradycardia.[1] In our study, bradycardia occurred in seven patients in group C but did not affect MAP. A possible explanation is that the low dose of clonidine used was not sufficient to induce marked sympatholysis.

Clonidine produces dose-dependent sedation.[1] The duration and intensity of postoperative sedation in our study was similar in the two groups. Interestingly, the four patients who experienced sedation in group C were among the seven patients who experienced bradycardia. Therefore, the occurrence of sedation could be indicative of systemic spread of clonidine.

Sympathetic outflow to the urinary tract promotes an increase in urethral resistance and depresses detrusor contraction, favouring urinary retention. Therefore, clonidine facilitates micturition.[5] There was no significant difference in time to first micturition between groups. We hypothesize that the small dose of clonidine given caudally was unlikely to have a peripheral effect on the bladder.

A study conducted in human volunteers failed to demonstrate any important effect of epidural clonidine on resting respiratory control.[6] Accordingly, respiratory variables were not monitored in our study.

Seven patients in the clonidine group experienced bradycardia without MAP disturbance compared with none in the saline group. Although delayed onset of haemodynamic effects has not been observed after clonidine for analgesia,[1] more specific evaluations would be valuable before using caudally administered clonidine for outpatient surgery.

In summary, we have demonstrated that addition of clonidine 75 µg to caudally administered local anaesthetics significantly prolonged the duration of postoperative analgesia after anal surgery in adults, with minimal side effects. Therefore, clonidine may be a potentially useful drug when prolonged postoperative analgesia is required after caudal block in adults.

References

1 Eisenach JC, De Koch M, Klimscha W. Alpha 2 adrenergic agonists for regional anesthesia. *Anesthesiology* 1996; **85**: 655–74
2 Jamali S, Monin S, Begon C, *et al.* Clonidine in pediatric anesthesia. *Anesth Analg* 1994; **78**: 663–6
3 Klimscha W, Chiari A, Michalek-Sauberer, et *al.* The efficacy and safety of a clonidine/bupivacaine combination in caudal blockade for pediatric hernia repair. *Anesth Analg* 1998; **86**: 54–61
4 Constant I, Gall O, Gouyet I, *et al.* Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. *Br J Anaesth* 1998; **80**: 294–8
5 Gentili M, Bonnet F. Spinal clonidine produces less urinary retention than spinal morphine. *Br J Anaesth* 1998; **76**: 872–3
6 Eisenach JC, Detweiler D, Hood D. Hemodynamic and analgesic actions of epidurally administered clonidine. *Anesthesiology* 1993; **78**: 277–87

British Journal of Anaesthesia **84** (3). 403–4 (2000)

Preparation for regional anaesthesia induces changes in thrombelastography

H. Gorton[1], G. Lyons[1] and P. Manraj[2]

[1]*Obstetric Anaesthesia, Level 5 Gledhow Wing, St James' University Hospital, Leeds LS9 7TF, UK.*
[2]*Department of Anaesthetics, Hull Royal Infirmary, Hull HU3 2JZ, UK*

The effects of crystalloid and colloid infusions on coagulation measured by thrombelastography (TEG) present a confused picture. The influence of environmental factors may explain the disparity between previous studies. We studied two groups of 20 women presenting at term for elective Caesarean section. In the first group, TEG analysis was performed before and after infusion of Gelofusine 500 ml over 15 min. The second group was treated in the same way except that subjects did not receive fluid. We found significant changes in *r* and *k* values in both groups, suggesting enhanced coagulation. As hypercoagulable changes were also seen in the group that did not receive fluid preload, the hypothesis that moderate haemodilution causes hypercoagulability must be questioned. The influence of environmental factors can explain differences reported between *in vivo* and *in vitro* studies.

Br J Anaesth 2000; **84**: 403–4

Keywords: measurement techniques, thrombelastography; blood, coagulation; anaesthetic techniques, regional; anaesthesia, obstetric

Accepted for publication: September 13, 1999

Reports of the effects of crystalloid and colloid infusions on coagulation measured by thrombelastgraphy (TEG) are ambiguous. Two *in vitro* studies found that coagulation was enhanced[1 2] and two found the reverse.[3 4] *In vivo* studies showed either no change[5] or changes attributed to hypercoagulability.[6] Similar changes are seen in pregnancy, where a hypercoagulable state develops. This is secondary to increased concentrations of procoagulants, especially fibrinogen, and factors II, VII, VIII, X and XI, and decreased concentrations of natural anticoagulants such as protein S. The associated TEG changes are reduced *r* and *k* values, and increased α angle and maximum amplitude (MA).[6]

The influence of environmental factors may be one explanation for the disparity between *in vivo* and *in vitro* studies. In this observational study, we have assessed the effect of environmental factors with and without gelatine preload on coagulation measured by TEG, before spinal anaesthesia for Caesarean section.

Methods and results

After obtaining approval from the Ethics Committee and informed consent, we studied two groups of 20 ASA I or II patients, presenting with uncomplicated pregnancies at 36–40 weeks' gestation for elective Caesarean section with regional anaesthesia. Patients with pre-existing hypertension or gestational hypertension (diastolic pressure >90 mm Hg), pre-existing haematological disorders, history of aspirin, warfarin, heparin or magnesium treatment, or diabetes mellitus were excluded.

In all women a 16-gauge cannula was inserted into a forearm vein and an initial blood sample was obtained for TEG analysis. The first 2 ml of each blood sample was discarded to avoid contamination by tissue thromboplastin, before using 0.36 ml for analysis. Each sample was analysed within 4 min of venepuncture. The samples were native whole blood, and were analysed using disposable cups and pins. Subsequently, subjects were studied sequentially in two groups.

In group 1 (n=20), colloid (Gelofusine) 500 ml was given over 15 min. A second sample was obtained from the contralateral arm via a 22-gauge cannula after infusion. The only intervention between the two blood samples was administration of fluid. In group 2 (n=20), the same procedure was performed except that no fluid was given between the two samples. All women were prepared for double space combined epidural–spinal anaesthesia. This was performed in a standard manner according to established practice.

To detect a 30% difference in *r* values with a power of 0.9 and 0.05 significance level, we calculated that 20 patients would be needed in each group. TEG variables were compared before and after preload using paired *t* tests with SPSS 7.1 for windows. Unpaired *t* tests were used to compare changes in TEG variables between groups. P<0.05 was considered significant.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Differences between the first and second samples of four TEG variables (mean (95% confidence intervals (CI) of the difference)) in the preload and control groups

	Mean difference 0–15 min	95% CI of difference	*P*
Preload group (n=20)			
r (mm)	7.7	3.22, 12.3	0.002
k (mm)	2.57	1.3, 3.9	0.001
α angle (°)	–4.35	–9.2, 0.5	0.076
MA (mm)	–0.45	–4.7, 3.84	0.83
Control group (n=20)			
r (mm)	9.8	4.4, 15.3	0.001
k (mm)	1.8	–1.5, 3.6	0.05
α angle (°)	–3.8	–7.7, 0.13	0.05
MA (mm)	–2.9	–5.6, –0.18	0.038

Patient characteristics in group 1 were: mean age 29.4 (range 19–38) yr, height 158.15 (SD 8.06) cm, weight 71.25 (12.44) kg and median gestation 38 [range 37–41] weeks; six had singleton pregnancies and two had twins. Characteristics in group 2 were: age 30.5 (20–39) yr, height 163.9 (6.03) cm, weight 78.25 (15.12) kg and gestation 38 [37–39] weeks; three had singleton pregnancies and one had twins. There were no clinically important differences between groups.

Differences in TEG variables with and without preload are shown in Table 1; r and k values were significantly shortened (P<0.05) in the preload group. In the control group, r and k were significantly reduced and MA was increased (P<0.05). There were no significant differences in the magnitude of the changes between groups.

Comment

We have shown that TEG variables (r and k) were reduced significantly over a 15-min period in women awaiting spinal anaesthesia for elective Caesarean section, whether or not an i.v. infusion was given. It was not possible to attribute changes in coagulation to the effects of preload alone. TEG changes were in keeping with those attributed previously to enhanced coagulation.[6] The magnitude of the changes was not clinically significant.

We hypothesize that siting an i.v. cannula, attachment of monitoring devices and a 15-min waiting period adjacent to our operating theatre were sufficient to influence coagulation. Some of the changes may have been a result of increased circulating catecholamines, which cause platelet degranulation and enhanced platelet aggregation.[7] Changes in platelet function have been shown to correlate only with changes in MA[8] and because we also reported changes in r and k values, this cannot be regarded as a complete explanation. Although it is known that large volumes of Gelofusine inhibit platelet function, our data did not provide evidence for this.

Previous *in vivo* studies were performed using varying degrees of haemodilution and fluid types, either in volunteers or in patients suffering blood loss during surgery. None independently assessed incidental factors.

Changes after preload which indicate hypercoagulation have been attributed to haemodilution which is believed to alter the balance of the activities of thrombin and antithrombin III so that thrombin becomes the more active.[1] This hypothesis must be questioned. We propose that changes in *in vivo* studies[6] may be attributed to environmental influences acting on coagulation.

References

1 Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–14

2 Ruttmann TG, James MFM, Wells KF. Effect of 20% in vitro haemodilution with warmed buffered salt solution and cerebrospinal fluid on coagulation. *Br J Anaesth* 1999; **82**: 110–11

3 Egli GA, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DK. Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. *Br J Anaesth* 1997; **78**: 684–9

4 Mardel SN, Saunders FM, Allen H, *et al.* Reduced quality of clot formation with gelatin-based plasma substitutes. *Br J Anaesth* 1998; **80**: 204–7

5 Karoutsos S, Nathan N, Lahrimi A, Grouille D, Feiss P, Cox DJA. Thrombelastography reveals hypercoagulability after administration of gelatin solution. *Br J Anaesth* 1999; **82**: 175–7

6 Ruttmann TG, James MFM, Aronson I. In-vivo investigation into the effects of haemodilution with hydroxyethyl starch and normal saline on coagulation. *Br J Anaesth* 1998; **80**: 612–16

7 Sharma SK, Philip J. The effect of anaesthetic techniques on blood coagulability in parturients as measured by thromboelastography. *Anaesth Analg* 1997; **85**: 82–6

8 Orlikowski CEP, Rocke DA, Murrar WB, *et al.* Thrombelastographic changes in preeclampsia and eclampsia. *Br J Anaesth* 1996; **77**: 157–61

British Journal of Anaesthesia 84 (3): 405–6 (2000)

Rectally administered dimenhydrinate reduces postoperative vomiting in children after strabismus surgery

A. Schlager*, G. Mitterschiffthaler and F. Pühringer

Department of Anaesthesia and Intensive Care Medicine, Division of Anaesthesia, Leopold Franzens University of Innsbruck, Austria

**Corresponding author: Department of Anaesthesia and General Intensive Care Medicine, Anichstraße 35, A-6020 Innsbruck, Austria*

We have investigated the effectiveness of rectally administered dimenhydrinate on postoperative vomiting in children undergoing strabismus surgery, in a double-blind, randomized, placebo-controlled study. In one group, dimenhydrinate 50 mg was administered rectally 30 min before starting anaesthesia, whereas in the control group, placebo suppositories were given. Children who received dimenhydrinate showed a significantly ($P<0.001$) lower incidence of vomiting (15%) than those in the control group (75%). We conclude that rectal administration of dimenhydrinate is an effective means of reducing postoperative vomiting in children undergoing strabismus surgery.

Br J Anaesth 2000; **84**: 405–6

Keywords: anaesthesia, paediatric; pharmacology, dimenhydrinate; vomiting, postoperative; vomiting, incidence; vomiting, antiemetics; surgery, ophthalmological

Accepted for publication: September 16, 1999

Postoperative vomiting (POV) is a common problem after strabismus surgery in children with an incidence of 40–88%.[1 2] Numerous studies have been performed to examine different antiemetics for their effectiveness in decreasing the incidence of POV after strabismus surgery. The H_1 antagonist dimenhydrinate is an inexpensive but rarely investigated antiemetic. When administered i.v., reports on the effects of dimenhydrinate in the prevention of POV in children undergoing strabismus surgery or adenotonsillectomy have been inconclusive.[3 4]

In this study, we have examined the antiemetic effect of preoperative rectal administration of dimenhydrinate in children undergoing strabismus surgery compared with a placebo group.

Methods and results

The study was approved by the Ethics Committee of the University of Innsbruck, Austria. Written informed consent was obtained from the parents of all children. We studied 40 children, ASA I, aged 3–12 yr, undergoing strabismus surgery. We excluded those with gastric or intestinal diseases, emesis and/or vomiting in the previous week and those who received any medical therapy immediately before surgery.

In this double-blind, prospective study, each child was allocated randomly to one of two groups. Children in group A received dimenhydrinate 50 mg rectally, 30 min before induction of anaesthesia; children in group B received a placebo suppository.

All patients were allowed solid food or clear fluids up to 6 h before anaesthesia. Oral premedication with midazolam 0.35 mg kg^{-1} (maximum 10 mg) and atropine 0.02 mg kg^{-1} was given 1 h before transfer to the operating room. For painless placement of an i.v. cannula, each child received 5% EMLA cream (Astra, Austria) on a vein in the left cubita or on the back of the left hand.

Strabismus repair was performed under general anaesthesia by the same surgeon. After standard monitors were attached, anaesthesia was induced with thiopental 5 mg kg^{-1} i.v. and fentanyl 2 μg kg^{-1} i.v. To facilitate intubation, rocuronium 0.6 mg kg^{-1} was given i.v. Anaesthesia was maintained with 1.5–2.5% sevoflurane and 66.6% nitrous oxide in oxygen under controlled ventilation. Fluid deficit was replaced by infusion of a mixture of three parts Ringer's lactate solution and two parts 5% dextrose. Immediately after arriving in the recovery room, all patients received paracetamol suppositories 10 mg kg^{-1} for postoperative analgesia.

The incidence of vomiting over 24 h after induction of anaesthesia was recorded by the nursing staff in the recovery room and on the ward. After surgery, all patients remained in the clinic for at least 24 h. If any patient vomited more than once, the ward nurses administered antiemetic rescue therapy (dimenhydrinate 50 mg suppositories).

Data were analysed using Fisher's exact test to determine

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Patient characteristics and incidence of postoperative vomiting (mean (SD or range) or number (%))

	Dimenhydrinate ($n = 20$)	Placebo ($n = 20$)	*P*
Age (yr)	6.5 (4–11)	5.9 (3–11)	ns
Sex (M/F)	10/10	11/9	ns
Weight (kg)	24 6 (9 1)	21.8 (6.1)	ns
Anaesthesia duration (min)	74 (16)	69 (17)	ns
Surgery duration (min)	54 (17)	48 (16)	ns
No. of muscles repaired	2.9 (0.9)	2 5 (0 8)	ns
Incidence of POV within 24 h	3/20 (15%)	14/20 (70%)	0 001

the incidence of vomiting and the unpaired *t* test to analyse patient characteristics. $P<0.05$ was regarded as statistically significant.

There were no significant differences between groups for age, sex, ASA status, weight, height, duration of anaesthesia, duration of surgery or number of repaired muscles (Table 1).

Compared with the placebo group, the incidence of vomiting was significantly lower in the dimenhydrinate group ($P<0.001$). Within the first 24 h after surgery, vomiting occurred in three children (15%; 95% CI 2.15–32%) in the dimenhydrinate group and in 14 (70%; 95% CI 48–92%) in the placebo group (Table 1).

Within the first 24 h, the overall incidence of vomiting in the dimenhydrinate group was lower (eight times in three children) than in the placebo group (62 times in 14 children). In the dimenhydrinate group, one of the three children who vomited received antiemetic rescue medication compared with nine of 14 children in the placebo group.

Comment

We have demonstrated that dimenhydrinate, administered rectally 30 min before induction of anaesthesia, reduced the incidence of POV in children after strabismus surgery. Previous studies reported contradictory results on the effectiveness of dimenhydrinate as an antiemetic in children. Dimenhydrinate 0.5 mg kg^{-1} i.v., given at induction of anaesthesia, caused a significant reduction in POV in children undergoing strabismus surgery (30% in the dimenhydrinate group and 65% in the placebo group).[4] However, Hamid and colleagues[3] found no significant difference in the incidence of POV in children after adenotonsillectomy compared with placebo (79% in the dimenhydrinate group, 82% in the placebo group).

Our results correspond to the findings of Vener and colleagues.[4] Children who received dimenhydrinate had significantly ($P<0.001$) less POV during the 24 h in hospital than those in the placebo group (15% in the dimenhydrinate group and 70% in the placebo group). In our study there were no adverse side effects, such as sedation, hypotension, adverse CNS reactions or skin reactions, in children who received dimenhydrinate.

Acknowledgements

We thank the nursing staff of the paediatric ward of the Clinic for Ophthalmology and Optometry, Innsbruck.

References

1 Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 24–32S

2 Tramer M, Moore A, McQuay H. Prevention of vomiting after paediatric strabismus surgery: a systematic review using the numbers-needed-to-treat method. *Br J Anaesth* 1995; **75**: 556–61

3 Hamid SK, Selby IR, Sikich N, Lerman J. Vomiting after adenotonsillectomy in children: a comparison of ondansetron, dimenhydrinate, and placebo. *Anesth Analg* 1998; **86**: 496–500

4 Vener DF, Carr AS, Sikich N, Bissonnette B, Lerman J. Dimenhydrinate decreases vomiting after strabismus surgery in children. *Anesth Analg* 1996; **82**: 728–31

British Journal of Anaesthesia 84 (3): 407–10 (2000)

BJA

CASE REPORTS

Postpartum headache after epidural blood patch: investigation and diagnosis

G. M. Stocks[1], D. J. A. Wooller[1], J. M. Young[2] and R. Fernando[3]*

[1]Department of Anaesthetics and [2]Department of Radiology, Whittington Hospital, Highgate Hill, London N19 5NF, UK. [3]Department of Anaesthetics, Royal Free Hospital, Pond Street, London NW3 2QG, UK

**Corresponding author*

Use of an epidural blood patch to treat spinal headache after accidental dural puncture is well recognized. The high success rate associated with this practice has been questioned and it is not uncommon for patients to suffer recurring headaches after a supposedly successful blood patch. We describe a patient in labour who suffered accidental dural puncture, and whose headache was treated twice with an epidural blood patch. Despite this, the headache persisted. The case highlights the difficulty in the diagnosis of headache in the postnatal period in patients who have had regional analgesia and the importance of considering an alternative pathology, even if epidural blood patching has been successful. In this case, a diagnosis of cortical vein thrombosis was made. The incidence, presentation, aetiology and treatment of this rare condition is described.

Br J Anaesth 2000; **84**: 407–10

Keywords: complications, dural puncture; complications, thrombosis; anaesthetic techniques, epidural; anaesthesia, obstetric

Accepted for publication: October 15, 1999

Use of an epidural blood patch to treat spinal headache after accidental dural puncture is well recognized,[1] and although the success rate is generally quoted to be as high as 90%,[2] there is evidence to suggest that this may be over optimistic.[3–5] Certainly, it is not uncommon for a patient to complain of recurrence, having had their initial spinal headache treated with an epidural blood patch. There are no clear guidelines in the literature regarding the number of times an epidural blood patch should be performed in the same patient, but each time the procedure is repeated the patient is at risk of complications.

This case report describes such a clinical dilemma. The differential diagnosis of postpartum headache is discussed and consideration of other pathologies as a cause of persistent headache after epidural blood patch is emphasized.

Case report

A previously healthy 20-yr-old, gravida 1, para 0 woman was admitted to the delivery suite at term in active labour. Apart from one migraine attack some years ago, she had little significant medical history and her pregnancy had been normal. Two hours later, she requested epidural analgesia. I.v. access was obtained and, under sterile conditions using the loss of resistance to saline technique, a 16-gauge Tuohy needle was inserted into the L2–3 interspace. Unfortunately, accidental dural puncture occurred. The needle was removed and resited in the L3–4 interspace where the epidural catheter was placed successfully. A test dose of 0.5% bupivacaine 2.5 ml was administered with no untoward effects, but shortly after she progressed to the second stage of labour and had a spontaneous vaginal delivery of a healthy infant.

She remained well after delivery and continued to do so for the next 24 h. However, on the second day postpartum, she developed an occipital headache and neck pain, which were both relieved by lying down. She was apyrexial, with no focal neurology, and arterial pressure was normal As a spinal headache was the obvious diagnosis, an epidural blood patch was performed under aseptic conditions using 18 ml of autologous blood placed at L2–3. Within 2 h, all symptoms had resolved, she was mobilizing well and was discharged from hospital that evening.

On day 3 postpartum, the headache returned with similar intensity and again with a definite postural element. She was readmitted to hospital and underwent a second epidural

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

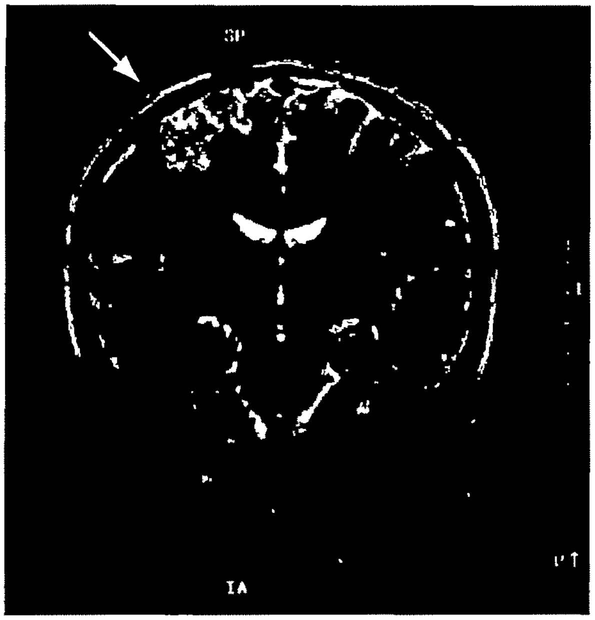


Fig 1 Coronal T2-weighted image showing high signal in part of the right cortex, consistent with cortical oedema and cortical vein thrombosis (arrow).

blood patch on day 4 postpartum, with 20 ml of autologous blood. This successfully resolved all of her symptoms, and she was discharged on day 5 postpartum. That afternoon she returned to hospital with a persistent occipital headache. However, this time it was more intermittent and throbbing with less of a postural element. It was not typical of a low pressure spinal headache and another epidural blood patch was thought to be inappropriate.

After admission her headache worsened, with additional symptoms of increasing confusion and sedation. At this point a neurological opinion was sought. As there was no focal neurology or papilloedema, the neurologist considered that migraine was the most likely diagnosis in view of the one episode she had suffered in the past. Conservative treatment with analgesics and i.v. fluid administration to prevent dehydration was advised.

That night the patient suffered four generalized grand mal seizures. These were controlled with diazepam i.v. Examination revealed no focal neurology, hypertension or evidence of eclampsia, and laboratory investigations were normal. The following morning (day 7 postpartum) she underwent a computerized tomography (CT) scan and magnetic resonance imaging (MRI). The former was not diagnostic but the MRI revealed an obvious lesion in the right cortex consistent with a diagnosis of cortical vein thrombosis (Fig. 1). She was commenced on oral phenytoin and transferred to the neurology unit. A diagnostic lumbar puncture was performed, and cerebral spinal fluid (CSF) examination revealed an increased protein concentration of 1.62 g litre^{-1}, a white cell count of 22 (mm^3)$^{-1}$ and a normal glucose concentration. CSF was blood stained with a red cell count of 1500 (mm^3)$^{-1}$. She had a full coagulant screen to exclude protein C, protein S and antithrombin III deficiencies, which if present can cause hypercoagulability. This was found to be normal. She was also negative for lupus anticoagulant, autoantibodies and antiphospholipid antibodies.

Table 1 Differential diagnoses of persistent headache in the puerperium

- Spinal headache after regional anaesthesia
- Non-specific
- Migraine
- Pregnancy-induced hypertension
- Meningitis
- Cerebral tumour
- Subarachnoid haemorrhage
- Subdural haematoma
- Cerebral vein thrombosis

Despite the presence of cortical vein thrombosis, it was decided not to commence anticoagulation therapy in view of the xanthochromia: she continued to be treated with i.v. fluids, analgesics and phenytoin. On this management, she made a full recovery and was discharged home. Review in the postnatal clinic 4 weeks later showed her to be well, but with significant memory loss about the events. It was decided that she should avoid the oral contraceptive pill, use an alternative form of contraception and that if she became pregnant again, she would need anticoagulation.

Discussion

The success rate of epidural blood patch to treat spinal headache is commonly quoted to be as high as 90%.[2] However, other studies have shown success rates of only 60–70%.[3–6] In the light of a possible overestimate of the effectiveness of epidural blood patch, how should the anaesthetist manage a patient who has returned with recurring headache after successful treatment with epidural blood patch? Should another epidural blood patch be performed with the risks of infection, repeat dural puncture and repeat failure, or should a conservative approach be adopted, the headache investigated further and other causes excluded?

The common and serious causes of persistent headache in the puerperium after regional anaesthesia are shown in Table 1. A thorough history is important to exclude other possible diagnoses before assuming that the headache is of spinal origin. In our patient, because the nature of her headache had changed, we felt that a third epidural blood patch was inappropriate and obtained a neurological opinion.

Spinal headache

Spinal headache typically presents 24–48 h postpartum with throbbing fronto-occipital pain which is relieved by lying flat. Associated symptoms include dizziness, tinnitus, hearing impairment, blurred or double vision, photophobia and neck stiffness. Physical examination is usually unremarkable. However, a discriminatory test described by Gutsche,[7] which involves application of firm manual pressure around the abdomen of the seated patient, can produce transient relief.

Non-specific headache and migraine

Non-specific headache is common after childbirth, occurring in 39% of mothers in the first week postpartum.[8] Migraine tends to improve in pregnancy but it can recur early after delivery. Headache typically is severe, throbbing in nature and often unilateral. It can be associated with nausea, vomiting and photophobia, and can even present with focal neurology.

Pregnancy-induced hypertension

Headache is usually associated with high blood pressure and in patients with pregnancy-induced hypertension, other symptoms may also be present, such as visual disturbances, nausea, vomiting or epigastric tenderness. Clinical examination may demonstrate hypertension, peripheral oedema and brisk reflexes. Investigations may reveal proteinuria, deteriorating renal function, increased liver enzymes and urate, and a coagulopathy.

Meningitis

Bacterial and aseptic meningitis have been reported after epidural,[9] spinal[10] and combined spinal–epidural[11] techniques and also after epidural blood patching.[12] Typical symptoms include headache, fever, nausea and vomiting, neck stiffness and an increased white cell count. CSF examination may distinguish between the two causes. With bacterial meningitis, CSF glucose is reduced and microscopy and culture of micro-organisms may be positive, whereas in aseptic meningitis, CSF glucose is normal with no organisms seen on microscopy or culture.

Much of the symptomatology associated with these conditions is very similar and it is often necessary to use CT and MRI scanning to exclude some of the rarer causes of postpartum headache listed in Table 1.

Cerebral tumour

Although rare, headache in the postpartum period caused by a cerebral tumour has been reported.[13] The headache is typically dull in nature and can be accompanied by signs of increased intracranial pressure such as nausea, vomiting and seizures.

Subarachnoid haemorrhage

This occurs in one to five cases per 10 000 pregnancies and presents typically with severe occipital headache, nausea, vomiting and depressed consciousness. The condition can be similar to that of pre-eclampsia because both are associated with hypertension. However, CT scanning can be diagnostic, the hallmark being an increased density of the CSF spaces caused by blood.

Subdural haematoma

Intracranial subdural haematoma may occur acutely or over a more chronic period after dural puncture.[14] CT is the investigation of choice in the acute situation, often revealing a high density crescent of fresh blood, concave on the deeper surface. As the haematoma ages it becomes 'isodense' on CT, and MRI is then the more sensitive investigation for detection and optimal delineation.[15]

In our case, when the patient suffered four generalized seizures, a CT scan was performed first to exclude a subarachnoid haemorrhage or subdural haematoma; an MRI scan was performed which revealed changes of a cerebral vein thrombosis limited to the cortical veins (Fig. 1).

Cerebral vein thrombosis

This condition is very rare, with an incidence of 8.9 cases per 100 000 deliveries.[16] In the most recent report on *Confidential Enquiries into Maternal Deaths*, there were only two deaths from cerebral vein thrombosis, both associated with deep vein thrombosis.[17] Cerebral vein thrombosis has a variable presentation but typically includes headache which may be gradual in onset or sudden, similar to a subarachnoid haemorrhage.[18] Headache can be accompanied by other neurological symptoms such as focal, multi-focal or generalized seizures, coma, hemiparesis or bilateral papilloedema.[19] In up to 26% of cases, CT scan is normal[20] but MRI is a more sensitive test, achieving a diagnosis in 90% of cases. However, if this is unsuccessful, MR venography, together with MRI, is sufficient to allow diagnosis in almost all cases and can be used for follow-up after treatment has been instigated.[21]

The aetiology of cerebral vein thrombosis is uncertain but the procoaguable state of pregnancy is a predisposing factor. Also, many patients have an inherited thrombophilia[22] and should undergo a thrombophilia screen. In our case, we believe that the cerebral vein thrombosis occurred after the second epidural blood patch, when the nature of the headache changed, and although it is not a recognized complication of epidural blood patch, this is the second such case to be reported.[23]

Cerebral vein thrombosis can be treated with anticoagulation therapy for 2–3 months, although this is controversial because of the risk of promoting further bleeding into an area of haemorrhagic infarct. In our case, anticoagulation was avoided because lumbar puncture revealed the presence of red blood cells. However, this could have occurred as a result of the two epidural blood patches.

In summary, this case serves to highlight the difficulty of diagnosis of persistent postpartum headache after epidural blood patch, and the importance of considering other possible pathologies.

References

1 Gormley JB. Treatment of postspinal headache. *Anesthesiology* 1960; **21**: 565–6

2 Abouleish E, Vega S, Blendinger I, Tio TO. Long-term follow-up of epidural blood patch. *Anesth Analg* 1975; **54**: 459–63

3 Berger CW, Crosby ET, Grodecki W. North American survey of the management of dural puncture occurring during labour epidural analgesia. *Can J Anaesth* 1998; **45**: 110–14

4 Taivalnen T, Pitkanen M, Tuominen M, Rosenberg PH. Efficacy of epidural blood patch for postdural puncture headache. *Acta Anaesthesiol Scand* 1993; **37**: 702–5

5 Stride PC, Cooper GM. Dural taps revisited. A 20 year survey from Birmingham Maternity Hospital. *Anaesthesia* 1993; **48**: 822–3

6 Williams EJ, Bealieu P, Fawcett WJ, Jenkins JG. Efficacy of epidural blood patch in the obstetric population *Int J Obstet Anesth* 1999; **8**: 105–9

7 Gutsche BB. Lumbar epidural analgesia in obstetrics: taps and patches. In: Reynolds F, ed. *Epidural and Spinal Blockade in Obstetrics*. London: Balliere Tindall, 1990; 95–106

8 Stein G, Morton J, Marsh A, *et al.* Headaches after childbirth. *Acta Neurol Scand* 1984; **69**: 74–9

9 Ready LB, Helfer D. Bacterial meningitis in parturients after epidural anesthesia. *Anesthesiology* 1989; **71**: 988–90

10 Lee JJ, Parry H. Bacterial meningitis following spinal anaesthesia for Caesarean section. *Br J Anaesth* 1991; **66**: 383–6

11 Harding SA, Collis RE, Morgan BM. Meningitis after combined spinal–epidural anaesthesia in obstetrics. *Br J Anaesth* 1994; **73**: 545–7

12 Berga S, Trierweiller MW. Bacterial meningitis following epidural anaesthesia for vaginal delivery. *Obstet Gynecol* 1989; **74**: 437–9

13 Boyd AH, Pigston PE. Postpartum headache and cerebral tumour. *Anaesthesia* 1992; **47**: 450–1

14 Pavlin DJ, McDonald JS, Child B, Rusch V. Acute subdural hematoma—an unusual sequela to lumbar puncture. *Anesthesiology* 1979; **51**: 338–40

15 Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial haematomas: imaging by high field MR. *Radiology* 1985; **157**: 87–93

16 Lanska DJ, Kryscio RJ. Peripartum stroke and intracranial venous thrombosis in the National Hospital Discharge Survey. *Obstet Gynecol* 1997; **89**. 413–18

17 Department of Health Welsh Office, Scottish Office Department of Health, Department of Health and Social Services, Northern Ireland. *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996*. London: HMSO

18 De-Bruijn SF, Stam J, Kappelle LJ. Thunderclap headache as first symptom of cerebral venous sinus thrombosis. CVST Study Group. *Lancet* 1996; **348**: 1623–5

19 Srinivasan K. Cerebral venous and arterial thrombosis in pregnancy and puerperium. A study of 135 patients. *Angiology* 1983; **34**: 731–46

20 Anxionnat R, Blanchet B, Dormont D, et *al.* Present status of computerized tomography and angiography in the diagnosis of cerebral thrombophlebitis cavernous sinus thrombosis excluded. *J Neuroradiol* 1994; **21**: 59–71

21 Lafitte F, Boukobza M, Guichard JP, et *al.* MRI and MRA for diagnosis and follow-up of cerebral venous thrombosis (CVT). *Clin Radiol* 1997; **52**: 672–9

22 Bray RL, Coull BM. Cerebral venous thrombosis. Role of activated protein C resistance and factor V gene mutation. *Stroke* 1996; **27**: 1719–20

23 Borum SE, Naul LG, McLeskey CH. Postpartum dural venous sinus thrombosis after postdural puncture headache and epidural blood patch. *Anesthesiology* 1997; **86**: 487–90

British Journal of Anaesthesia **84** (3). 411–3 (2000)

Patient-controlled analgesia in labour using remifentanil in two parturients with platelet abnormalities

J. A. Thurlow[1] and P. Waterhouse

Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK
[1]Present address: Frenchay Hospital, Frenchay, Bristol BS16 1LE, UK

Two term parturients with documented platelet abnormalities presented to the delivery suite in labour. Because regional analgesic techniques were contraindicated, we elected to use patient-controlled i.v. remifentanil for pain relief. The patient-controlled analgesia (PCA) device was programmed to give a bolus dose of remifentanil 20 μg over 20 s with a lockout time of 3 min, and no background infusion. Analgesia was reported as very good by the mothers and by the attending midwives. There were no adverse neonatal sequelae. If there are facilities to monitor the neonate and mother, this method of analgesia may prove useful in those patients where regional techniques are not possible, but further research is needed to ascertain its safety and appropriateness in such circumstances.

Br J Anaesth 2000; **84**: 411–3

Keywords: analgesia, obstetrics; analgesia, patient-controlled; analgesics opioid, remifentanil; blood, platelets

Accepted for publication: October 4, 1999

Obstetric anaesthetists are not infrequently confronted by patients with known coagulopathies requesting pain relief in labour, but for whom epidural is contraindicated. In the following two patients, patient-controlled analgesia (PCA) using remifentanil provided adequate pain relief.

Case reports

Patient No. 1

A 26-yr-old, 66-kg primigravida was admitted to the antenatal ward for investigation of falling platelets and hypertension. During the first trimester, the patient had a platelet count of 173×10^3 ml^{-1} and arterial pressure of 110/60 mm Hg. At 32 weeks' gestation, her platelet count was 118×10^3 ml^{-1} and arterial pressure remained unchanged. At 37 weeks' gestation, a full blood count showed a platelet count of 113×10^3 ml^{-1} and arterial pressure was 130/90 mm Hg. Platelet count was monitored weekly and decreased progressively, reaching 73×10^3 ml^{-1} at 39 weeks' gestation, when arterial pressure was 140/85 mm Hg. She was admitted for closer monitoring and investigation.

Urea and electrolyte concentrations, urate concentrations, liver function tests and measures of blood clotting were normal. Arterial pressure became persistently increased, reaching 160/100 mm Hg, and the decision was made to induce labour. Her daily platelet count had decreased to 59×10^3 ml^{-1}, but increased a little to 96×10^3 ml^{-1} at the time of induction.

Labour was induced using a prostaglandin E_2 pessary and then continued with an infusion of Syntocinon i.v. Before infusion was started, analgesia for labour was discussed fully with the patient by a senior anaesthetist. Although platelet count had increased to 96×10^3 ml^{-1} by the time of induction, epidural analgesia was not performed because of the previous low fluctuating platelet count and consequent risk of epidural haematoma. She was offered remifentanil i.v. using a PCA device. Full instructions were given to the patient and attending midwife, and an anaesthetist was available at all times. Remifentanil 1 mg was diluted to a volume of 50 ml with normal saline, resulting in a concentration of 20 μg ml^{-1} of solution. The PCA pump (Graseby 2400) was set to deliver a bolus dose of remifentanil 20 μg with a lockout time of 3 min. A cannula was sited in a forearm vein, and a dedicated line was used. There was continuous monitoring of the fetus and mother. The first stage of labour proceeded for 6 5 h, augmented by Syntocinon i.v. The second stage lasted 13 min. The fetal heart showed good variability throughout labour and maternal oxygen saturation was normal with an $F_{I_{O_2}}$ of 21%. A live baby girl weighing 3240 g was delivered, with Apgar scores of 9 at 1 min and 10 at 5 min. No neonatal resuscitation was required.

The PCA was used for the last 2 h of labour. During this time she made 49 demands of which 37 were good, and received a total dose of remifentanil 740 μg. The patient was assessed continually throughout labour to ensure she had adequate pain relief, and questioned shortly after

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

delivery about the analgesia she had received. She experienced no pruritus, no nausea or vomiting, but was drowsy between contractions. She commented that this was not unpleasant as it wore off very quickly. She was very pleased with her analgesia, commenting that although it did not take away all of the pain of labour, it made it manageable and that she had felt more in control.

The baby was transferred to the neonatal intensive care unit after delivery as the platelet count in cord blood was 52×10^3 ml^{-1}. The mother was discharged to the post-natal ward shortly afterwards and advised to remain in hospital for 72 h. Repeat platelet counts on both mother and neonate returned to normal levels and the mother's arterial pressure returned to normal within a few days. Mother and baby were discharged home on the third day after delivery.

Patient No. 2

A 25-yr-old, 61-kg primagravida was referred to the obstetric anaesthetic service at 32 weeks' gestation to discuss analgesia during labour. She was known to have chronic idiopathic thrombocytopenic purpura (platelet count 60–80×10^3 ml^{-1}). During the pregnancy, her platelet count declined steadily to 46×10^3 ml^{-1} at the 23rd week of pregnancy. She was also a known asthmatic, controlled with salbutamol and beclomethasone inhalers. When she was seen in the outpatient clinic by the senior obstetric anaesthetist, her platelet count was 48×10^3 ml^{-1}, and after full discussion with explanation of the risks and benefits, as outlined for patient No. 1, she was offered the use of patient-controlled remifentanil.

She presented to the labour ward at 34 weeks' gestation with spontaneous rupture of membranes and in active labour. Platelet count had decreased further to 34×10^3 ml^{-1}. She used Entonox for the first 3 h before remifentanil PCA was set-up, with explanations and monitoring as in patient No. 1. The cannula was sited in a forearm vein, and a dedicated line was used. She used PCA for the next 3 h until full cervical dilation. During this time she made 74 demands of which 47 were good, and received a total dose of remifentanil 940 µg. She used Entonox for the 15-min second stage. A live baby girl, weighing 1720 g, was born by normal vaginal delivery, with Apgar scores at birth of 9 at 1 min and 10 at 5 min. No neonatal resuscitation was required.

When questioned the following day, she described analgesia as very good. She had no pruritus, nausea or vomiting. The baby was transferred to the neonatal intensive care unit for supplementary feeding and remained in hospital for 10 days, before being discharged home.

Discussion

Epidural analgesia for labour is not recommended if the platelet count is less than 100×10^3 ml^{-1} (normal $>150\times10^3$ ml^{-1})[1] because of the risk of epidural haematoma and resulting neurological damage. Non-pharmacological forms of analgesia, such as breathing exercises and transcutaneous nerve stimulation (TENS), are inadequate for established and augmented labour. Entonox may also be inadequate. Pethidine is the most widely used opioid but causes marked sedation.[2]

Patient-controlled analgesia techniques are not new to obstetrics: it is the standard delivery system for Entonox. Pethidine has been given by PCA[3] and there are case reports of fentanyl PCA in labour.[4 5] Remifentanil may have advantages over other opioids when used as PCA because of its rapid onset and offset times, allowing better matching of analgesia to the intermittent pains of labour without accumulative side effects.

Remifentanil has an effect-site half-life for analgesia of 1.3 min,[6] which gives it a rapid onset time, and it is hydrolysed rapidly by red blood cell and tissue esterases.[7] Its effects are reversed by naloxone.[8] It has been used as an i.v. infusion during non-urgent Caesarean section as an adjunct to epidural anaesthesia. It crosses the placenta but appears to be rapidly metabolized, redistributed, or both, with no clinically adverse effects on the neonate.[9] Remifentanil has similar potency to fentanyl,[10] which is why we chose our scheme of a 20-µg bolus.[5] Both patients remained comfortable using this scheme and they were both satisfied with their analgesia. Since we made our observations, we are aware of a case report of patient-controlled analgesia using remifentanil in the parturient with thrombocytopenia but much larger doses were used.[11]

In summary, we used remifentanil i.v. by PCA as a method of managing pain during labour in two patients where epidural analgesia was contraindicated. I.v. PCA with a short-acting drug should be better than intermittent i.m. injections because it avoids the pain of injection and allows better matching of analgesic delivery to the pain. Further research needs to be carried out in this field to further ascertain its safety and appropriateness as it may prove to be a suitable method of pain management in labour.

Acknowledgement

We thank Dr N Goodman for help with the preparation of the manuscript.

References

1 Roibin SH, Abott D, Musclow E, Papsin F, Lie LM, Freedman J. Epidural anesthesia in pregnant patients with low platelet counts. *Obstet Gynecol* 1988; **71**: 918–20

2 Olofsson Ch, Ekblom A, Ekman-Ordeberg G, Hjelm A, Irestedt L. Lack of analgesic effect of systemically administered morphine or pethidine on labour pain. *Br J Obstet Gynaecol* 1996; **103**: 968–72

3 Evans JM, McCarthy JP, Rosen M, Hogg MIJ. Apparatus for patient-controlled administration of intravenous narcotics during labour. *Lancet* 1976; **1**: 17–18

4 Kleiman SJ, Weisel S, Tessler MJ. Patient-controlled analgesia (PCA) using fentanyl in a parturient with a platelet function abnormality. *Can J Anaesth* 1991; **38**: 489–91

5 Rosaeg OP, Kitts JB, Koren G, Byford LJ. Maternal and fetal effects of intravenous patient-controlled fentanyl during labour in a thrombocytopenic parturient. *Can J Anaesth* 1992; **39**: 277–81

6 Glass PSA, Hardman D, Kamiyama Y, *et al.* Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: Remifentanil (G187084B). *Anesth Analg* 1993; **77**: 1031–40

7 Selinger K, Nation RL, Smith GA Enzymatic and chemical hydrolysis of remifentanil. *Anesthesiology* 1995; **83**: A385

8 Amin HM, Sopchak AM, Esposito RN, Graham CL, Batenhorst RL, Camporesi EM. Naloxone reversal of depressed ventilatory response to hypoxia during continuous infusion of remifentanil. *Anesthesiology* 1993; **79**: A1203

9 Kan RE, Hughes SC, Rosen MA, Kessin C, Preston PG, Lobo EP. Intravenous remifentanil. Placental transfer, maternal and neonatal effects. *Anesthesiology* 1998; **88**: 1467–74

10 James MK, Feldman PL, Schuster SV, Bilotta JM, Brackeen MF, Leighton HJ. Opioid receptor activity of G187084B, a novel ultra-short acting analgesic in isolated tissues. *J Pharmacol Exp Ther* 1991; **259**: 712–18

11 Jones R, Pegrum A, Stacey RGW. Patient-controlled analgesia using remifentanil in the parturient with thrombocytopenia. *Anaesthesia* 1999; **54**: 461–5

British Journal of Anaesthesia 84 (3): 414–6 (2000)

Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine

D. S. Ure*, M. A. Gillies and K. S. James

Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow G4 0SF, UK
**Corresponding author*

We report the safe use of remifentanil as part of the anaesthetic technique in a patient undergoing major head and neck surgery who was being treated for depressive illness with the non-specific monoamine oxidase inhibitor (MAOI) phenelzine.

Br J Anaesth 2000; **84**: 414–6

Keywords: sympathetic nervous system, MAO inhibitors; surgery, otolaryngological; analgesics opioid, remifentanil

Accepted for publication: October 4, 1999

Anaesthesia and perioperative management of patients treated with monoamine oxidase inhibitors (MAOI) is problematic. The decision to discontinue antidepressant treatment before surgery, to avoid potential interactions with drugs used during anaesthesia, or to continue treatment to avoid relapse of illness may be difficult. The principal drugs implicated in severe interactions with MAOI are sympathomimetic agents and the opioid analgesic pethidine. We describe the management of a patient undergoing major surgery in whom remifentanil was used as part of a balanced anaesthetic technique.

Case report

A 56-yr-old, 80-kg male with a squamous cell carcinoma of the piriform fossa presented for pharyngolaryngectomy and free jejunal flap repair. His past medical history included severe depression resistant to standard drug therapy for which he was treated with the non-specific MAOI phenelzine 15 mg twice daily. He had hepatitis C infection in the past but was not a carrier and had abused alcohol previously but had been abstinent for 3 yr. Other medications were zopiclone for insomnia, and co-codamol. He smoked 20 cigarettes per day. Preoperative investigations (full blood count, urea and electrolytes, liver function tests and ECG) were normal. An examination under general anaesthesia 2 weeks previously for tumour staging had been uneventful. At that time he had been given propofol and alfentanil for induction of anaesthesia, and oxygen, nitrous oxide and isoflurane for maintenance. After discussion with the patient about potential risks, we decided to continue treatment with phenelzine up to the time of surgery, primarily to avoid relapse of his depressive illness. Also, with this type of surgery, where adequate arterial pressure is critical to ensure survival of the jejunal free flap, we were concerned that stopping treatment might predispose him to perioperative hypotension.[1]

Temazepam 20 mg was given as premedication. I.v. access was established and ECG, pulse oximetry and intra-arterial arterial pressure monitoring were started. Anaesthesia was induced with sevoflurane in oxygen. Manual ventilation of the lungs was possible and vecuronium 6 mg was given to enable nasotracheal intubation. A left subclavian line and urinary catheter were inserted and additional monitoring of CVP, urine output, temperature (core and peripheral) and gas analyser were established. Fluid and body warmers were used.

Anaesthesia was maintained with oxygen, air, isoflurane and an infusion of remifentanil. The initial remifentanil infusion rate was 0.02 $\mu g\ kg^{-1}\ min^{-1}$. The patient remained haemodynamically stable and normothermic, and thereafter the infusion rate was titrated against his autonomic response to surgical stimulation. The maximum infusion rate required was 0.2 $\mu g\ kg^{-1}\ min^{-1}$.

During periods of minimal surgical stimulation, hypotension was treated with fluids and incremental methoxamine i.v. Five 0.1-mg test doses of methoxamine were given initially to check that hypertension did not occur secondary to interaction with phenelzine. After 0.5 mg had been given without complication, further doses of 1 mg were given as necessary, without adverse effects. A total of 26 mg were used during the procedure.

Surgery lasted 12 h. Blood loss was approximately 3000 ml and total fluid replacement was 15 litre (crystalloid solution 14.5 litre and concentrated red blood cells 2 u.). Anaesthesia was uneventful. In particular, there were no clinical signs to indicate adverse interaction with the MAOI treatment. Arterial pressure and urine output were well maintained throughout.

The infusion of remifentanil was stopped towards the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

end of surgery and spontaneous respiration established. Morphine 1-mg i.v. boluses to a total of 15 mg were given over the final hour of surgery for postoperative analgesia. Another 20 mg were given on awakening and the patient was rational, cooperative and pain-free before transfer to the high dependency unit. Patient-controlled analgesia with morphine was used for postoperative analgesia. His postoperative progress was uneventful and he was discharged home 3 weeks after surgery.

Discussion

Monoamine oxidase (MAO) is an enzyme found principally on outer mitochondrial membranes. There are two isoenzymes, MAO-A and MAO-B, each with different substrate specificities. Substrates for MAO-A include epinephrine, serotonin (5-HT) and norepinephrine, while MAO-B preferentially deaminates amines such as benzylamine and phenylethanolamine. Both forms deaminate tyramine and dopamine. Substrate specificity is relative, however, and is concentration dependent. Distribution of the isoenzymes differs between tissues. Approximately 60% of MAO activity in the brain is of the A-subtype. MAO-B predominates in the liver and lungs.[2]

The monoamine oxidase inhibitors were the first effective antidepressant drugs. Their use declined with the introduction of more effective drugs with fewer side effects, but they are still used in the treatment of atypical and refractory depression and several other disorders (e.g. eating disorders, migraine, chronic pain syndromes).[2]

Non-specific MAOI (e.g. phenelzine, isocarboxazid) cause irreversible inhibition of both MAO subtypes. Inhibition of non-neuronal MAO is responsible for the 'cheese reaction', a hypertensive crisis induced by eating foods rich in substances such as tyramine which displace norepinephrine from vesicular storage. Normally, MAO inactivates monoamines absorbed from foods and this indirect sympathomimetic response is prevented. The effects of indirectly acting sympathomimetic amines (e.g. ephedrine, metaraminol) can be potentiated in the same way. Specific MAO-A inhibitors (e.g. clorygyline) should be less likely to potentiate indirectly acting sympathomimetics because MAO-B in tissues should be spared. However, interactions have occurred despite this theoretical advantage.[3 4]

An adverse interaction is also seen with pethidine, secondary to block of neuronal 5-HT uptake by this drug. A potentially fatal syndrome characterized by agitation, hypertension or hypotension, hyperthermia, convulsions and coma may occur, although pethidine has been given to patients receiving MAOI without adverse effects. Other opioid analgesics appear to be safe for patients receiving MAOI. Morphine has been used to treat headache in patients with the cheese reaction.[5] Fentanyl and alfentanil have also been used safely, although a case report has implicated the use of high-dose fentanyl during cardiac surgery in the postoperative death of a patient treated with an MAOI.[6]

To minimize the possibility of adverse reactions in patients receiving MAOI who present for surgery, discontinuation of therapy 2 weeks before operation has traditionally been recommended,[7–9] although this policy has been challenged as evidence of safe anaesthetic techniques in these patients emerged.[10 11] The risks and benefits of discontinuing therapy need to be considered for each patient on an individual basis. In our case, we felt that the risk of relapse of depressive illness and the potential for perioperative hypotension if treatment was stopped outweighed the risk of drug interaction if therapy was continued. The patient was fully informed of the options available and agreed with our recommendation to continue treatment.

Remifentanil is an ideal opioid for intraoperative use for the type of surgery we performed. It has a short elimination half-life of 5–8 min because of rapid elimination by plasma esterases[12] and the context-sensitive half-life does not change, even after prolonged infusion, so the effects of the drug wear off rapidly after cessation of infusion. This process is unaffected by hepatic and renal function. The infusion rate can be titrated rapidly to adjust to changes in surgical stimulus. This is valuable during this type of operation as there are long periods during neck dissection and vascular anastomoses where stimulation is minimal. If high-dose, longer-acting opioids are used to dampen responses to surgical stimuli earlier in the procedure, hypotension can ensue during periods of minimal stimulation, and emergence from anaesthesia may be delayed because of accumulation of drug.

A second advantage in using remifentanil is that MAC values of volatile anaesthetic agents are markedly reduced. There is nothing in the pharmacological profile of remifentanil to suggest that it would interact adversely with MAOI, but a search of the MEDLINE database from 1988–1999 did not produce any report of its use in patients receiving these drugs. We felt that remifentanil would have significant benefits in terms of haemodynamic stability and recovery from anaesthesia in our patient, and that adverse interaction with phenelzine was unlikely.

References

1 Sprung J, Distel D, Grass J, Bloomfield EL, Lavery IC. Cardiovascular collapse during anesthesia in a patient with preoperatively discontinued chronic MAO therapy *J Clin Anesth* 1996; **8**: 662–5

2 Wells D, Bjorksten A. Monoamine oxidase inhibitors revisited. *Can J Anaesth* 1989; **36**: 64–74

3 Lader MH, Sakalis G, Tansella M. Interaction between sympathetic amines and a new monoamine oxidase inhibitor. *Psychopharmacologica* 1972; **18**: 118–23

4 Pare CMB. The present status of monoamine oxidase inhibitors. *Br J Psychiatry* 1985; **146**: 576–84

5 Brown DD, Waldron DH. An unusual reaction to tranylcypromine. *Practitioner* 1962; **189**: 83–5

6 Noble WH, Baker A. MAO inhibitors and coronary artery surgery: a patient death. *Can J Anaesth* 1992, **39**: 1061–6

British Journal of Anaesthesia **84** (3): 417–424 (2000)

Correspondence

Exhaustion of an ABEK nitric oxide absorber

Editor,—The ABEK HgCO NO-P3 filter (Drager) has been described as an effective method of scavenging nitric oxide and nitrogen dioxide.[1] The filter contains microglass fibres coated with copper and chromium salts, and the catalysts, manganese dioxide and copper oxide. This article describes its use with an Evita 2 ventilator with a minute volume of 6.1 litre min^{-1}. Proximal nitric oxide concentrations of 55–70 ppm were maintained in 100% oxygen. Measurement of environmental nitrogen dioxide concentrations over a 170-h period peaked at 0.4 ppm. The recommendation was that this filter could be used safely for up to 1 week.

Since this report, we have successfully used this filter. Readings taken close to the filter are usually undetectable, with a maximum recorded concentration of nitrogen dioxide 0.4 ppm. If a patient remains on nitric oxide for longer than 7 days, the filter is changed routinely. However, we would like to describe a case in which the filter became exhausted within 72 h.

A 16-yr-old was admitted to the PICU with respiratory failure after bone marrow transplantation. A presumed diagnosis of pneumocystitis pneumonia was made and he was treated with oxygen via facial mask CPAP and high-dose co-trimoxazole. His condition deteriorated and an open lung biopsy was undertaken after which he required mechanical ventilation. He continued to deteriorate rapidly and nitric oxide 20 ppm was commenced. His lungs were ventilated at a minute volume of 16 litre min^{-1}, $F\text{I}_{\text{O}_2}$ 100%, tidal volume 800 ml, ventilatory frequency 20 bpm and I:E ratio 1:1. Airway pressures were 40/10 cm H_2O. Expired nitrogen dioxide concentrations were measured using an electrochemical sensor (with PTFE membrane). Concentrations remained less than 2 ppm at all times. After 72 h there was a sudden increase in the environmental nitrogen dioxide level. After replacement of the scavenging filter, environmental nitrogen dioxide concentrations decreased rapidly to zero.

Our report demonstrates the need to measure environmental nitrogen dioxide concentrations, particularly in the vicinity of the filter, as the filter may become exhausted more quickly than reported previously. Compared with the results of Squire, Knightley and Petros,[1] this patient was receiving a lower inspired nitric oxide concentration but had a much greater minute volume. The manufacturers estimate that the filter will take 4–5 litre of nitric oxide with a flow rate of 8 litre min^{-1}. However, our patient had twice this flow rate. We suggest that when patients have such a high minute volume while using nitric oxide, the ABEK filter should be changed at least every 72 h.

C. G. Stack
M. Gibbons
J. A. Nuttall
M. Quinton
Paediatric Intensive Care
Sheffield Children's Hospital
Western Bank
Sheffield, UK

1 Squire S, Knightley R, Petros AJ. An effective method of scavenging nitric oxide *Br J Anaesth* 1996; **77**: 432–4

Costs of sevoflurane and propofol anaesthesia

Editor,—We read with interest the article by Smith and colleagues on the costs of sevoflurane and propofol anaesthesia.[1] In today's cost-conscious climate, cost analyses such as the one published recently by Smith and colleagues are worthwhile. The authors have shown that induction and maintenance of anaesthesia with propofol is more expensive than induction and maintenance with sevoflurane. However, we are concerned with some of their conclusions and would like to make a few general comments

First, we were disappointed that, contrary to their claims, the authors had not included all direct and indirect costs. Rowe recently published a cost comparison of propofol and inhalation anaesthesia[2] and we were surprised that this article, which contained a more comprehensive cost analysis, was not cited. The most glaring cost that the authors ignored was that of overnight admission. We accept that their admission rate was low and unlikely to alter overall costs significantly, but it would have been helpful to include some estimate of the additional costs associated with the admission of the two patients who received inhalation anaesthesia only. Notwithstanding the costs arising from i v. infusion pumps, other costs that should have been mentioned include the capital and maintenance costs of sevoflurane vaporizers and the scavenging apparatus.

Second, we believe that the use of nitrous oxide for all groups was a flaw in the study design. The environmental problems associated with the use of nitrous oxide were ignored completely.[3] Furthermore, nitrous oxide is known to increase the incidence of nausea and vomiting,[4 5] and this has made interpretation of the results more difficult. There was already a significantly lower incidence of nausea and vomiting in patients who received propofol, but omission of nitrous oxide may have resulted in an even lower incidence. Ventilation with oxygen and air would probably have increased propofol use and cost, but this has to be balanced against the benefit of emesis-free recovery. Treatment of PONV comprised only one drug administration in the propoful group, whereas 21 doses of different drugs were required to treat patients in the sevoflurane nitrous oxide group.

Third, in the discussion, the authors present their study as confirming that sevoflurane 'is an acceptable day-case anaesthetic'. Later they assert that propofol was associated with 'few clinical benefits in terms of speed or quality of recovery'. Sevoflurane, however, was associated with a six-fold higher incidence of nausea and a 12-fold higher incidence of vomiting than induction and maintenance of anaesthesia with propofol. Given that postoperative emesis is a concern patients have before surgery,[6] it is difficult to see how induction and maintenance of anaesthesia with sevoflurane can be considered 'acceptable'. Surely this markedly lower incidence of nausea and vomiting associated with propofol is 'a significant clinical benefit'? In fact, one in 10 patients in the sevoflurane group did not wish to receive the same anaesthetic during future surgery. In the analysis of 'cost', should not the cost to the individual patient in terms of personal comfort also rate?

Finally, it is worth pointing out that anaesthesia where nitrous oxide is used is, by definition, not 'total i.v. anaesthesia', as mentioned in the last paragraph of the article.

A Absalom
A. Troy
University Department of Anaesthesia
Glasgow Royal Infirmary, UK

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

1 Smith I, Terhoeve PA, Hennart DA, *et al.* A multicentre comparison of the costs of anaesthesia with sevoflurane or propofol. *Br J Anaesth* 1999; **83**: 564–70
2 Rowe WL. Economics and anaesthesia. *Anaesthesia* 1998; **53**: 782–8
3 Shaw ADS, Morgan M. Nitrous oxide, time to stop laughing? *Anaesthesia* 1998; **53**: 213–15
4 Hartung J. Twenty four of twenty seven studies show a greater incidence of emesis associated with nitrous oxide than with alternative anesthetics. *Anesth Analg* 1996; **83**. 114–16
5 Divatia JV, Vaidya JS, Badwe RA, Hawalder RW. Omission of nitrous oxide during anesthesia reduces the incidence of post-operative nausea and vomiting. A meta-analysis. *Anesthesiology* 1996; **85**: 1055–62
6 Orkin FK. What do patients want? Preferences for immediate recovery. *Anesth Analg* 1992; **74** (Suppl.): 225

Editor,—Drs Absalom and Troy make some interesting comments. We attempted to include all of those direct and indirect costs which we could measure. Rowe[1] included the costs associated with nursing time, operating time and other staff costs, although these were average values for the day unit and not individually measured costs. Indeed, these costs are extremely difficult to measure objectively and there is no certainty that alterations in time actually result in increases or savings in staff costs in real life. Savings will probably only be realized if fewer staff are employed (or hours are reduced) and extra costs will only be incurred if extra staff or paid overtime are required.

Two patients in group 3 were indeed admitted overnight. The reasons for these admissions were described briefly in our article and must be considered before their inclusion in the cost analysis. The first patient (who had been recovering satisfactorily for some time) developed somnolence and respiratory depression only after administration of fentanyl to treat postoperative pain. This problem may well have been avoided by the use of an alternative form of analgesia or a lower dose of fentanyl. It did not appear to be related to the use of sevoflurane. The second patient was operated on relatively late in the day and arrived in the recovery unit shortly before the day unit was due to close. Because of the late hour, the patient was transferred to an inpatient surgical ward and admitted overnight. Performing this operation at a more appropriate hour of the day would have prevented this admission. It was therefore felt that neither of these admissions were directly attributable to the anaesthetic which the patient received and so the cost of admission was not included. Postoperative nausea and vomiting played no part in either admission.

With regard to other indirect costs, we did not include the costs of vaporizers as these items are generally supplied 'free' by the anaesthetic vendor. This is rarely the case with i.v. infusion pumps. While not really free, the vaporizer price is already reflected in the drug purchase cost. Modern sevoflurane vaporizers require very little servicing. In the UK, Blease recommend two service visits per year, at a total cost (including VAT) of £63.45 (Blease Medical, personal communication). This represents less than $0.5 per working day and was therefore negligible for our purposes. Scavenging is used universally in all hospitals. The best evidence for possible hazards from trace concentrations (and therefore the best justification for scavenging) comes from nitrous oxide. As nitrous oxide was common to all three groups, the cost of scavenging was a common cost to all three groups (as was the anaesthetic machine, anaesthetist, breathing circuit, etc.).

We do not consider inclusion of nitrous oxide a flaw in this study. We did discount the environmental impact of this and every other drug, technique and item of equipment used; that is a separate issue entirely. We included nitrous oxide in all groups as it is used commonly with both i.v. and inhalation anaesthesia. Either technique *could* have been conducted without nitrous oxide and it is pointless to speculate on the effects of this measure on nausea and vomiting, drug consumption, etc. Omission of nitrous oxide would probably have reduced PONV in all groups, although a recent meta-analysis showed the effect to be quite weak.[2]

In their third point, Absalom and Troy have apparently forgotten that our study involved three anaesthetic groups, the third receiving sevoflurane after propofol induction. This group had a statistically similar incidence of nausea and similar recovery times, despite significantly greater costs compared with the propofol induction and maintenance group. It was in the context of these group comparisons that we considered propofol to have 'few clinical benefits'. The six- and 12-fold increased incidence of nausea and vomiting, respectively, were in the sevoflurane induction group. Despite this problem, 90% of these patients considered the technique 'acceptable', although the proportion was higher in the two other groups.

Multiple factors contribute to nausea and vomiting, and unfortunately we did not establish that all other potential causes of these unpleasant side effects were evenly distributed between groups. In addition to nitrous oxide, the use of intraoperative fentanyl may have been relevant. In my routine day-case practice, I use sevoflurane for induction and maintenance but do not administer fentanyl. To date, 342 patients having similar procedures to those in this study have received this technique, the incidence of postoperative nausea or vomiting is currently 5.6%, with only 1.2% requiring antiemetic therapy.

Naturally, patient satisfaction is important, but difficult to assign a financial value. Dissatisfaction was no more common in patients with nausea than in those without. Some element of the dissatisfaction may have been related to the relative inexperience of some investigators with inhaled induction. Again, in day-to-day practice (as opposed to the artificial environment of a randomized, controlled trial), use of sevoflurane for induction and maintenance is very well tolerated.

Finally, the last point is conceded. Total i.v. anaesthesia involves only i.v. drugs, although the term is commonly (and wrongly) used as 'shorthand' for anaesthesia induced and maintained with propofol. I apologize for this mistake.

I. Smith
Keele University
Stoke-on-Trent
Staffordshire, UK

1 Rowe WL. Economics and anaesthesia. *Anaesthesia* 1998; **53**: 782–8
2 Tramèr M, Moore A, McQuay H. Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia *vs* omitting nitrous oxide *vs* total i.v. anaesthesia with propofol. *Br J Anaesth* 1997; 78. 256–9

Editor,—I read with interest the report by Smith and colleagues of their multicentre comparison of sevoflurane and propofol for day-case anaesthesia.[1] I am concerned by the authors' interpretation of some of their data. Nausea occurred significantly more frequently in patients anaesthetized with sevoflurane alone (incidence 31.9%) than in those who received propofol–sevoflurane (7.4%) or propofol–propofol (5.6%). Sevoflurane was also associated with vomiting (incidence 17.4%, 8.6% and 0%, respectively, for patients receiving sevoflurane alone, propofol–sevoflurane and propofol–propofol). In addition, patients who underwent both induction and maintenance of anaesthesia with sevoflurane were significantly less likely to agree to receive the same anaesthetic again on a future occasion than those in whom anaesthesia was induced with propofol. I find these data difficult to reconcile with the comments in the discussion that 'sevoflurane, used either as a maintenance agent or for induction and maintenance of anaesthesia, is an acceptable day-case anaesthetic' and later that 'total i.v anaesthesia with propofol was ...... associated with few clinical benefits in terms of speed or quality of recovery'.

The authors comment at length in their discussion on both nausea and vomiting and patient preference, but appear to give these important patient-related end-points little priority in contrast with the small financial saving ($13.1 per case) associated with a sevoflurane–sevoflurane technique. Surely an equally valid interpretation of these data might reject sevoflurane as a day-case anaesthetic in favour of total i.v. anaesthesia with propofol, which in this study offered superior quality of recovery and improved patient preference at a modest additional cost.

Perhaps we should also consider what patients themselves think about postoperative nausea and vomiting (PONV). When previous investigators have done so, they reported that patients were more worried about PONV than about pain,[2] would tolerate some additional pain to avoid PONV[3] and ranked it as 'least desirable outcome' from a surgery/anaesthesia episode.[4]

The guide to contributors to the *British Journal of Anaesthesia* requires that 'There should be clear declaration of any financial or commercial interest which any author may have in the material'. The paper acknowledges financial support from Abbott Laboratories, the manufacturer of sevoflurane. However, we are not told whether the authors have received any lecture fees or other research support from the same source. Readers might find this information useful when evaluating this report.

J. R. Sneyd
Department of Anaesthesia
Derriford Hospital
Plymouth, UK

Conflict of interest

Dr Sneyd has received research support from Abbott Laboratories, the manufacturer of sevoflurane, and lecture fees and research support from AstraZeneca, the manufacturer of propofol.

1 Smith I, Terhoeve PA, Hennart DA, *et al.* A multicentre comparison of the costs of anaesthesia with sevoflurane or propofol. *Br J Anaesth* 1999; **83**: 564–70
2 Van Wijk MGF, Smalhout B. A postoperative analysis of the patient's view of anaesthesia in a Netherlands' teaching hospital. *Anaesthesia* 1990, **45**: 679–82
3 Orkin FK. What do patients want? Preferences for immediate postoperative recovery. *Anesth Analg* 1992; **74**: S225
4 Macario A, Weinger M, Carney S, Kim A, Garber A. Which clinical anesthesia outcomes patients find most undesirable? *Anesthesiology* 1998; **89** (Suppl.): A1330

Editor,—I thank Dr Sneyd for his interest in our article. All three anaesthetic techniques allowed rapid, smooth induction of anaesthesia, good intraoperative conditions and rapid recovery. By these criteria they were all acceptable. The incidences of nausea and vomiting were significantly higher in the sevoflurane induction and maintenance group only, and this is a cause for concern. Nevertheless, many cases were transient, occurring early in the recovery process, and not all required treatment. Although significantly more patients in this group would have chosen a different technique in the future, 90% still found their anaesthetic 'acceptable'. Furthermore, patients with PONV were no more likely to prefer an alternative future anaesthetic compared with those without these symptoms.

In criticizing our assertion that propofol anaesthesia was associated with few benefits, Dr Sneyd has taken our comments out of context. What we actually said was 'i.v. anaesthesia with propofol was more expensive than anaesthesia induced with propofol followed by sevoflurane (group 2), but was associated with few clinical benefits in terms of speed or quality of recovery'. This statement is true; in comparing the two groups, there were no significant differences in recovery times or incidence of nausea. We then went on to comment 'use of sevoflurane for induction and maintenance of anaesthesia (group 3) produced a further small reduction in costs ...... but was associated with a significant increase in postoperative nausea and vomiting, delay in ambulation (but not discharge) and reduction in patient satisfaction'.

Naturally, the patient's experiences and expectations are very important. However, this study made no allowances for various strategies which may reduce postoperative emesis, including omission of opioids from the volatile anaesthetic-based groups[1] and/or the use of prophylactic antiemetics. As for Dr Sneyd's alternative conclusion, while the additional cost of using propofol is indeed $13.1 per case ($12.2 from the propofol–sevoflurane group), the additional cost per case of PONV 'prevented' by propofol is $30.13 compared with sevoflurane induction and maintenance, and $85.40 compared with propofol–sevoflurane. These values are not quite so modest.

I am happy to disclose that I have previously received research funding from Abbott Laboratories (among others) and lecture fees from both Abbott and Astra-Zeneca. The original covering letter to the *British Journal of Anaesthesia* included the statement that 'some of the authors have received honoraria from Abbott for lecturing on an occasional basis'. It was therefore never our intention to conceal this information.

I. Smith
Keele University
Stoke-on-Trent
Staffordshire, UK

1 Shakir AAK, Ramachandra V, Hasan MA. Day surgery postoperative nausea and vomiting at home related to peroperative fentanyl *J One-day Surg* 1997; **6**(3): 10–11

Adverse effects of cannabis and cannabinoids

Editor,—This review article was timely.[1] It emphasized that in the young adult population we should be cognizant that 10–30% of 20–30-yr-olds may have used cannabis in the week before anaesthesia. Many obstetric patients do not admit to drug use, even on direct questioning (David Birnbach, personal communication 1999), and I am sure that this would apply to a request for an illegal drug history before anaesthesia. Should we therefore be screening all patients in this age group as the list of serious complications described in association with cannabis use would appear to present major anaesthetic risk? On the other hand, why have these central nervous depressant and cardiorespiratory stimulant effects not been manifest in multiple case reports in the anaesthetic literature? There are certainly case studies in association with cocaine abuse but not cannabis, yet cannabis is traceable for a longer period in body fluids.

Apart from normal clinical anaesthesia, where there has been no systematic investigation, the issue of studies of cannabis and cannabinoids should be considered. The majority of medical studies of cannabis as distinct from cannabinoids, have used non-naïve patients, thus the records of adverse effects are often in combination with an unknown quantity of cannabinoid material in tissues. The reluctance to use non-naïve subjects opens the question as to whether or not cannabis-naïve patients should enter, for example, long-term pain studies of tetrahydrocannabinol (THC) or cannabis plant material. However, THC, the main psychoactive cannabinoids in cannabis, is licensed for use in the USA and has met the requirements of the regulatory authorities. If the adverse effects of cannabis are caused by cannabinoids other than THC, these need to be identified. The warnings in the data sheet for THC include caution in patients known to have a history of substance abuse, cardiac disorders, psychiatric history and those receiving sedatives. This pales into insignificance when the list of adverse effects from commonly used drugs, such as non-steroidal analgesics, is examined in the *British National Formulary*.

What is required are standardized preparations of cannabinoids available for medicinal use. Then the focus can be on the adverse effects of a known amount of medicinal product rather than the broader issue of substance abuse.

A. Holdcroft
ICSM Hammersmith Hospital
London, UK

---

1 Ashton CH. Adverse effects of cannabis and cannabinoids. *Br J Anaesth* 1999; **83**: 637–49

Editor,—Dr Holdcroft raises some interesting questions concerning the widespread use of cannabis in the young population. Why, she asks, have adverse effects of cannabis in anaesthetic practice been so rarely reported, and should patients in the 20–30-yr-old age group who require an anaesthetic be screened routinely for drug use?

Unfortunately, as stated in the review, there are no systematic studies of cannabis effects on anaesthesia. The theoretical potential for risks is based largely on animal data and isolated clinical reports. Until definitive studies are undertaken, we do not know if the actual risks are minimal or if they have simply been under-recognized. In the present state of knowledge, it is unlikely that routine screening for cannabis use would be very informative (except as a warning of possible but unknown complications) Because of the very slow elimination of cannabinoids and their metabolites (which are still detectable in urine up to 1 month after a single dose) and the considerable degree of pharmacokinetic and pharmacodynamic tolerance developed in chronic users, there is a poor relationship between cannabinoid concentrations in body fluids and central or systemic effects. Clearly, further research is needed. This would be difficult and should involve current cannabis users compared with non-users in the same age groups.

Dr Holdcroft also asks whether cannabis-naive patients should enter clinical studies for therapeutic actions of cannabinoids. Her assertion that the majority of medical studies have used non-naive patients is mistaken. In the UK, the synthetic cannabinoid nabilone has been used for many years as an antiemetic for cannabis-naive patients undergoing cancer chemotherapy. Dronabinol, synthetic Δ^9-tetrahydrocannabinol (THC) in sesame oil, has been used similarly in the USA. The therapeutic and adverse effects of these cannabinoids for this indication are well known. Nabilone and dronabinol can be prescribed legally for other indications and have been used in several clinical studies for pain relief in diverse conditions, including cancer pain and multiple sclerosis, mostly in cannabis-naive patients (references cited in the review). These cannabinoids may have a potential in palliative care[1] and there is nothing to prevent interested anaesthetists setting up their own studies.

The pharmacology of other cannabinoids (there are more than 60 in herbal cannabis) is little known but promising new synthetic cannabinoids are under development[2] and a Clinical Cannabinoid Group has been set up by the Department of Health to examine the clinical use of standardized cannabinoids preparations.[3] The medical use of raw cannabis is not recommended[3] because of the known toxicity of the many non-cannabinoid constituents (about 340) which are broadly similar to and carry the same risks as those of smoked or ingested tobacco.

C. H. Ashton
Department of Psychiatry
University of Newcastle upon Tyne
Royal Victoria Infirmary
Newcastle upon Tyne, UK

1 Ashton H. Cannabis in palliative care. *CME Bulletin Palliative Medicine* 1999; **1**: 73–7
2 Pertwee RG. Pharmacology of CB_1 and CB_2 receptors. *Pharm Ther* 1997; **74**: 128–80
3 British Medical Association. *Therapeutic uses of cannabis*. U.K. Harwood Academic Publishers, 1997

Pulmonary aspiration of gastric contents in obstetrics

Editor,—I was most interested in the review article by Engelhardt and Webster,[1] particularly the sections dealing with obstetric patients. While pointing out the steady decline in maternal deaths from pulmonary aspiration reported by the *Confidential Enquiries into Maternal Deaths in the UK* from the 1960s to the 1990s, they failed to specify concurrent relevant changes in anaesthetic practice. Over the past 11 yr, since the introduction of atraumatic pencil-point spinal needles, there has been a dramatic increase in the use of spinal anaesthesia in the UK, although this has not been well documented.[2] One wonders if we would have seen the decline in mortality associated with aspiration over the past decade were it not for the concurrent reduction in the number of general anaesthetics.

The values quoted from the recent Norwegian audit[3] are correct, but it should be mentioned that the authors declared there had been a trend for increased spinal and epidural anaesthesia for Caesarean section in that country. Furthermore, all obstetric patients who aspirated did so during airway problems under general anaesthesia and, although there were no deaths, admission to intensive care was necessary.

When commenting on the incidence of pulmonary aspiration in obstetrics, Engelhardt and Webster focused on studies from the first world. However, maternal mortality in the first world pales into insignificance compared with the staggering figures for the third world.[4] Since the review has been published in an international journal of anaesthesia, it will be read by anaesthetists practising in the third world and I would suggest they be cautious about eschewing recommendations for reducing gastric volume and acidity. General anaesthesia is still the norm in obstetrics in many third world countries and two recent studies from Zululand and Zimbabwe have highlighted deaths caused by failures in airway management in which aspiration probably contributed to fatality.[5 6] Preventive measures are particularly important in the third world because there may not be resources for adequate treatment if aspiration does occur.

One interesting South African study[7] not mentioned in the review found that combining ranitidine and sodium citrate produced higher mean pH values from 1 h onwards compared with orogastric tube aspiration or sodium citrate, or both. This suggests that ranitidine should be administered earlier rather than later if Caesarean section is pending. A further advantage of ranitidine is that it increases lower oesophageal sphincter tone.[8]

The reviewers are to be commended for drawing attention to potential side effects of histamine receptor antagonists and proton pump inhibitors. A literature search on use of ranitidine in obstetrics revealed only three reports of anaphylactoid reactions[9–11] to oral and i.v. doses. Symptoms resolved after oxygen and a H1 blocker together with (in two cases) hydrocortisone; no patient required admission to intensive care. Given the widespread use of ranitidine in obstetrics, such reactions would seem to be extremely rare. Improved outcome through use of ranitidine and sodium citrate in obstetrics may not have been proven. To the best of my knowledge, improved outcome from the use of monitoring devices such as pulse oximetry in anaesthesia has not been proved either, but who would dare to suggest that this monitoring is unwarranted?

A. G. McKenzie
Department of Anaesthetics
Edinburgh Royal Infirmary
Edinburgh, UK

1 Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. *Br J Anaesth* 1999; **83**: 453–60
2 Brown GW, Russell IF. A survey of anaesthesia for Caesarean section. *Int J Obstet Anesth* 1995; **4**: 214–18
3 Soreide E, Bjornestad E, Steen PA. An audit of perioperative aspiration pneumonitis in gynaecological and obstetric patients. *Acta Anaesthesiol Scand* 1996; **40**: 14–19
4 Adamson P. Women: maternal mortality (a failure of imagination). In. *The Progress of Nations*. New York UNICEF, 1996; 2–9
5 Larson JV, Janowski KA, Krolikowski A Maternal mortality in hospitals in Zululand, July 1993–June 1994. *S Afr Med J* 1996; **86**: 424–30
6 McKenzie AG. Operative obstetric mortality at Harare Central Hospital 1992–94: an anaesthetic view. *Int J Obstet Anesth* 1998; **7**: 237–41
7 Brock-Utne JG, Rout C, Moodley J, Mayat N. Influence of preoperative gastric aspiration on the volume and pH of gastric contents in obstetric patients undergoing Caesarean section. *Br J Anaesth* 1989; **62**: 397–401
8 Brock-Utne JG, Downing JW, Humphrey D Effect of ranitidine given before atropine sulphate on lower oesophageal sphincter tone. *Anaesth Intensive Care* 1984; **12**: 140–2
9 Greer IA, Fellows K. Anaphylactoid reaction to ranitidine in labour. *Br J Clin Pract* 1990; **44**: 78
10 Barry JE, Madan R, Hewitt PB. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesthesia* 1992; **47**: 360–1
11 Powell JA, Maycock EJ. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesth Intensive Care* 1993; **21**: 702–3

Editor,—We thank Dr McKenzie for his interest in our article.[1] This review encompassed aspiration during all forms of anaesthesia and was intended to highlight the lack of evidence for the increasingly widespread practice of gastric content pH-raising prophylaxis. It was not aimed specifically at obstetric anaesthesia but the point is made in the review for the continued use of such agents in this particular area. It is, however, correct to point out that obstetric anaesthesia has seen a dramatic change in practice with a shift from general to regional anaesthesia, as recent studies in the USA and Germany document.[2–4]

The American study[4] showed a decrease in maternal mortality from 4.3 per million live births for 1979–1981 to 1.7 per million live births in 1988–1990, which was a result mainly of a decrease in mortality in patients who received regional anaesthesia from 8.6 to 1.9 per million regional anaesthetics, respectively. There was, however, an increase in mortality from 20 to 32.2 deaths per million patients receiving obstetric general anaesthesia during that period. The role of aspiration in these cases remains unknown.

Physiological changes in pregnancy may alter morbidity and mortality in the obstetric patient We are, however, not aware of any studies which show a decrease in either morbidity or mortality after the introduction of antacid or prokinetic medication or orogastric tube aspiration. Adequate anaesthetic training and shifting the emphasis from general to regional anaesthesia rather than simply relying on these unproved preventative measures is the way forward in both first and third world countries.

Finally, surely it is necessary to regularly reassess even the most basic principles in our clinical practice and move closer to evidence-based practice.

T. Engelhardt
N. R. Webster
Anaesthesia and Intensive Care
University of Aberdeen
Aberdeen, UK

1 Engelhardt T, Webster NR. Pulmonary aspiration of gastric contents in anaesthesia. *Br J Anaesth* 1999, **83**: 453–60
2 Wulf H, Stamer U. Aktuelle Praxis der Anasthesie zur Sectio caesarea an den deutschen Universitatskliniken. *Der Anesthetist* 1998; **47** 59–63
3 Chestnut DH. Anaesthesia and maternal mortality. *Anesthesiology* 1997; **86**: 273–6
4 Hawkins JL, Koonin LM, Palmer SK, Gibbs CP. Anesthesia related deaths during obstetric delivery in the United States, 1979–1990 *Anesthesiology* 1997; **86**: 277–84

Acoustic monitoring for neuromuscular block

Editor,—I read with interest the study of Dascalu and colleagues[1] on the use of acoustic monitoring for neuromuscular block Without wanting to discuss the value of this method, I would like to bring to the readers' attention that the authors overlooked a useful and versatile monitor of neuromuscular transmission already available for clinical use. The TOF-Guard and its successor the TOF-Watch (Organon Teknika/Biometer, Belgium) feature accelerography together with most available modes of stimulation, and display measured train-of-four (TOF) values. The TOF-Watch is no bigger than a usual nerve stimulator. The convenience and precision of these monitors have been established in several studies[2–4] and in clinical practice. Studies have shown that recovery to a TOF ratio of at least 0.7 is necessary to avoid postoperative complications[5] and that tactile evaluation cannot satisfactorily assess residual neuromuscular block.[6] Therefore, the use of a small monitor that displays TOF values is important.

Although for scientific purposes accelerography cannot be used interchangeably with mechanomyography, the observed differences are negligible in clinical use. I agree with Dascalu and colleagues[1] that mechanomyography, electromyography and, with the original larger monitor, accelerography, are inconvenient to use and/or costly. However, with the availability of monitors such as the TOF-Watch, introduction of a new method which differs markedly from standard monitoring, such as the reported acoustic method, is of purely scientific interest. This is emphasized even more by the fact that an 'easy to apply, yet accurate method of quantifying the degree of neuromuscular block' during clinical monitoring is already available.

K. S. Khuenl-Brady
Department of Anaesthesia and Intensive Care Medicine
University of Innsbruck
Innsbruck, Austria

1 Dascalu A, Geller E, Moalem Y, Manoah M, Enav S, Rudick Z Acoustic

monitoring of intraoperative neuromuscular block. *Br J Anaesth* 1999; **83**: 405–9

2 Loan PB, Paxton LD, Mirakhur RK, Connolly FM, McCoy EP. The TOF-Guard neuromuscular transmission monitor. A comparison with the Myograph 2000 *Anaesthesia* 1995; **50**: 699–702

3 Dahaba AA, Rehak PH, List WF. Assessment of accelerography with the TOF guard: a comparison with electromyography. *Eur J Anaesthesiol* 1997, **14**: 623–9

4 Greer R, Harper NJ, Pearson AJ. Neuromuscular monitoring by intensive care nurses: comparison of acceleromyography and tactile assessment. *Br J Anaesth* 1998, **80**: 384–6

5 Viby-Mogensen J, Roed J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41**: 1095–103

6 Fruergaard K, Viby-Mogensen J, Berg H, el Mahdy AM. Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. *Acta Anaesthesiol Scand* 1998; **42**. 1168–74

Editor,—Thank you for the opportunity to reply to Dr Khuenl-Brady.

The authors endorsing the use of a particular technique overlooked some of the data from our study as we compared accelerography with microphone acoustics and mechanomyography (see results). Our results are in accordance with previous data, demonstrating that acceleromyography has wide limits of agreement (−62 to +12%) and exhibits a bias of −25% relative to mechanomyography.[1] Another well controlled study concluded that acceleromyographic and mechanomyographic recordings of neuromuscular transmission cannot be used interchangeably because of different recovery courses.[2] Unlike the opinion expressed by Dr Khuenl-Brady, other authors have recommended that information from accelerography and mechanomyography should not be used interchangeably because of major differences between the methods.[3] Accordingly, it was shown that accelerography had wide and unacceptable limits of agreement and was more susceptible to drift than mechanomyography.[4] We would conclude that observed differences between mechanomyography and accelerography are far from being negligible in clinical use and that accelerography cannot be substituted for mechanical measurements, the present 'golden standard'.

We believe that acoustic myography is a method for daily clinical use by the anaesthetist, correlating closely with mechanical measurements, and which has the potential advantage of monitoring central muscles of respiration. We conclude that it is an easy to apply and *accurate* method of quantifying neuromuscular block when clinical monitoring is needed.

A Dascalu
Department of Physiology and Pharmacology
School of Medicine
Tel Aviv University
Tel Aviv, Israel
Z. Rudick
Department of Anaesthesiology
Ichilov Medical Center
Israel

1 McCluskey A, Meakin G, Hopkinson JM, Baker RD A comparison of acceleromyography and mechanomyography for determination of the dose–response curve of rocuronium in children. *Anaesthesia* 1997; **52**: 345–9

2 Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Pedersen HS, Severinsen IK, Schmidt MB. New equipment for neuromuscular transmission monitoring. A comparison of the TOF-Guard with the Myograph 2000. *J Clin Monit Comp* 1998; **14**: 19–27

3 Loan PB, Paxton LD, Mirakhur RK, Connolly FM, McCoy EP. The TOF-Guard neuromuscular-transmission monitor—a comparison with the Myograph-2000. *Anaesthesia* 1995; **50**: 699–702

4 Harper NJN, Martlew R, Strang T, Wallace M. Monitoring neuromuscular block by acceleromyography—comparison of the Mini-Accelograph with the Myograph-2000. *Br J Anaesth* 1994; **72**· 411–14

Bradycardia after administration of remifentanil

Editor,—Remifentanil is a recently introduced opioid with the desirable characteristics of a rapid onset and short duration of action.[1] Its use has been recommended for controlling the cardiovascular and intraocular pressure responses to tracheal intubation.[2 3] We report a case where its administration led to severe bradycardia.

An 82-yr-old woman, weighing about 70 kg, was scheduled for repair of a perforating eye injury after a fall. The only past medical history of note was hypertension. Medications included atenolol 50 mg, bendrofluazide 2.5 mg and aspirin 75 mg daily. The patient had received an uneventful general anaesthetic in 1998 for a bladder repair. Preoperative investigations were normal except that the ECG showed a sinus bradycardia of 45 beat min^{-1}. She arrived in the operating room in the afternoon having taken all her medications in the morning before her fall.

After placement of non-invasive monitors (arterial pressure cuff, ECG and pulse oximeter), and siting of an i.v. infusion of Hartmann's solution, the patient was given 100% oxygen. Anaesthesia was induced using a target-controlled infusion of propofol to a target of 2 $\mu g\ ml^{-1}$. A bolus dose of remifentanil 50 µg was administered over 1 min and the patient's lungs were ventilated with 100% oxygen. Heart rate decreased to 35 beat min^{-1} within 30 s of administration of remifentanil. Atropine 0.6 mg was administered i.v. The patient was given rocuronium 40 mg and the trachea intubated 60 s later The patient's heart rate remained at 35 beat min^{-1} and another dose of atropine 0.6 mg was given i.v. An infusion of remifentanil which was intended to be commenced after the bolus was not started. Heart rate decreased further to 31 beat min^{-1} and arterial pressure could not be recorded using the cuff. At this point, epinephrine, 0.5 ml (1:10 000) was given, resulting in a broad complex tachycardia, which was treated with lidocaine 100 mg i.v. The rhythm reverted to sinus bradycardia at a rate of 44 beat min^{-1} with an arterial pressure of 70/30 mm Hg. An arterial line was inserted and an infusion of epinephrine was started to maintain the patient's heart rate and arterial pressure.

A decision was made to defer surgery and transfer the patient to the ICU to be monitored, and to be reviewed by a cardiologist. The infusion of epinephrine was continued overnight. In view of a persistent bradycardia, the patient had a temporary pacing wire inserted before surgery the following day when she was anaesthetized uneventfully using propofol, rocuronium and sevoflurane. The patient was transferred to the care of the cardiologists, and was discharged after insertion of a permanent pacemaker.

The recommended bolus of remifentanil, according to the package insert, is 1.0 $\mu g\ kg^{-1}$ administered over 30–60 s, with a dose reduction in the elderly; our patient perhaps received a slightly large dose for her age. Laryngoscopy and intubation failed to increase heart rate. Others have also reported severe bradycardia in patients receiving beta-adrenergic receptor blocking agents and given remifentanil.[4 5] In the case reported by DeSouza, Lewis and TerRiet, the patient was receiving metoprolol and nitrates, had been premedicated heavily and had received remifentanil $1\ \mu g\ kg^{-1}$ followed by an infusion of $0.1\ \mu g\ kg^{-1}\ min^{-1}$ for 2–3 min[5] Concomitant administration of a neuromuscular blocking agent such as vecuronium with an opioid can lead to bradycardia. However, bradycardia occurred in our patient before administration of the blocker, and in any case rocuronium has a slight vagolytic action.

Opioid-induced bradycardia is generally accepted to be vagally mediated.[6] This effect seems to be exacerbated in the presence of beta-receptor blocking agents, and in this patient it appears that we may have unmasked a tendency to a bradyarrhythmia. This may have been the cause of the fall, which led to the initial injury to the eye.

We suggest that even a slow bolus of remifentanil may result in severe bradycardia in elderly patients receiving beta-receptor blocking drugs or with pre-existing bradycardia A slow infusion may be preferable and result in less haemodynamic disturbances

J E Reid
R. K Mirakhur
Department of Anaesthetics
The Queen's University of Belfast
Belfast, UK

1 Glass PSA, Hardman D, Kamiyama Y, *et al.* Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid. remifentanil (GI87084B). *Anesth Analg* 1993; **77**: 1031–40
2 McAtamney D, O'Hare R, Hughes D, Carabine U, Mirakhur RK. Evaluation of remifentanil for control of haemodynamic response to tracheal intubation. *Anaesthesia* 1998, **53**. 1223–7
3 Alexander R, Hill R, Lipham WJ, Weatherwax KJ, El-Moalem HE. Remifentanil prevents an increase in intraocular pressure after succinylcholine and tracheal intubation *Br J Anaesth* 1998; **81**: 606–7
4 Dershwitz M, Randel Gl, Rosow CE, et *al.* Initial clinical experience with remifentanil, a new opioid metabolised by esterases *Anesth Analg* 1995, **81**: 619–23
5 Desouza G, Lewis MC, TerRiet MF Severe bradycardia after remifentanil. *Anesthesiology* 1997; **87**: 1019–20
6 Reitan JA, Stengert KB, Wymore MC, Martucci RW. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia. *Anesth Analg* 1978; **57**: 31–6

Pulmonary haemorrhage after percutaneous paravertebral block

Editor,—With reference to the case report by Thomas, Sanders and Berrisford,[1] which described pulmonary haemorrhage as a complication of percutaneous paravertebral block when a 16-gauge Tuohy needle was inserted to a depth of 6 cm in the mid-thoracic region, I would like to make the following comments.

The Tuohy needle was inserted inappropriately deep for a mid-thoracic paravertebral block; identification of the paravertebral space with the loss of resistance technique may give a false negative result; and a 22-gauge Tuohy needle is the needle of choice for single-shot percutaneous paravertebral blocks

A full understanding of the anatomy is essential for safe use of any regional technique. When performing a paravertebral block, it is imperative to locate the transverse process of the vertebra, before advancing the needle into the paravertebral space. In the thoracic region, the spinous process of a vertebra lies in the same horizontal level as the transverse process of the vertebra below, because of the extreme angulation of the spinous processes. In adults, the transverse processes are located 2.5 cm lateral to the midpoint of the spinous processes. The skin to transverse process distance varies from 2–3 cm in the T5–6 region to 5 cm in the T1–2 region. However, there may be a small variation depending on the size of the patient. The paravertebral space lies anterior to the transverse processes and superior to the costotransverse ligaments, at a depth of 1 cm from the posterior surface of the transverse processes.

Loss of resistance with saline or air can be used to locate the space as the needle passes through the superior costotransverse ligament but may result in false negatives Scar tissue in the paravertebral space, or a previous thoracotomy, may interfere with the loss of resistance technique.

A 22-gauge Tuohy needle (B. Braun Medical Inc, Product code E2230T) is the needle of choice for single-shot percutaneous paravertebral blocks. It has the advantage of a small diameter. 1-cm markings to a depth of 8 cm so that the precise depth of the tip of the needle is always known and a blunt tip so that a 'pop' may be experienced as it passes through the costotransverse ligament. Unfortunately, this needle is not available in the UK, but can be imported by special arrangement by B. Braun Medical Inc

At Duke University Medical Center, all breast surgery is performed using percutaneous paravertebral blocks with sedation We have performed more than 1000 percutaneous blocks with no pneumothoraces and only two epidural spreads We would like to describe our technique First, choose which dermatomes will be involved in the operative field. For mastectomy with axillary dissection, we routinely block T1–T6. The patient is placed in the sitting position with their neck flexed, back arched and shoulders dropped forward. The spinous process of each level is identified and a mark is placed at its most superior aspect. From the midpoint of these marks a needle entry site is marked 2.5 cm lateral to each spinous process ipsilateral to the incision. These marks should overlie the transverse process of the immediately caudad vertebra. Using an aseptic technique, a 22-gauge 8-cm Tuohy needle attached via extension tubing to a syringe is inserted through the skin and advanced anteriorly in the parasagittal plane until it contacts the transverse process, which is 2–5 cm depending on the habitus of the patient. In the T6 region, the expected depth of the transverse process is 2–3 cm. Inserting the needle 1 cm past this predicted depth is allowed. If the transverse process is not identified at the appropriate depth, it is assumed that the needle tip lies between adjacent transverse processes, and the needle should not be advanced any deeper If bone is contacted at a point that seems too deep, this is probably a rib lying anterior to the transverse process. In both these cases, return the needle to the skin point, and search in a cephalad and then a caudal direction until the transverse process is successfully contacted. This depth is noted as the estimated distance to subsequent transverse processes. The needle is then withdrawn to the subcutaneous tissue and angled to walk onto the caudad edge of the transverse process by 1 cm. At thoracic level, it is common to appreciate a loss of resistance or a subtle 'pop' as the needle passes through the superior costotransverse ligament. After aspiration, 3–5 ml of local anaesthetic (0.5% bupivacaine or 0.5% ropivacaine with epinephrine 1 400 000) are injected at each level

Percutaneous paravertebral blocks can be safe and effective when performed in good hands. The complications of the block are minimized by a full understanding of the anatomy of the paravertebral space and identification of a safe pre-end-point (i.e. the transverse process).

R. P. Hill
St Richard's Hospital
Chichester, UK
R. Greengrass
Duke University Medical Center
Durham, NC, USA

1 Thomas PW, Sanders DJ, Berrisford RG. Pulmonary haemorrhage after percutaneous paravertebral block. *Br J Anaesth* 1999; **83**: 668–9

Editor,—Thank you for the opportunity to respond to the points raised by Drs Hill and Greengrass regarding our recent case report describing a case of pulmonary haemorrhage after a percutaneous paravertebral block. It was not the intention of this case report to give a detailed description of how a paravertebral block should be executed correctly. This has been eloquently described in several publications, two of which[1 2] were referred to in our original article. It goes without saying, however, that a sound knowledge of the relevant anatomy is a prerequisite for this and indeed any other regional or local anaesthetic technique being performed.

We would take issue with the comment made that the Tuohy needle was inserted inappropriately deep for a mid-thoracic paravertebral block. In a recently published article,[3] the depth from skin to paravertebral space in 86 female patients ranged from 3.1 to 6.0 cm. Similarly, Richardson and colleagues[4] reported a mean depth of the paravertebral space of 5 cm with an SD of 0.7 cm. The female patient in our case report was a relatively thick set individual, and while 6 cm is quite deep, it could not be considered to be outside the normal range.

Drs Hill and Greengrass comment that scar tissue in the paravertebral space may give a false negative result when using a loss of resistance to air technique We agree entirely—this was exactly the point we were illustrating in our case report. To our knowledge, this complication had not been documented before, which prompted us to report it.

As the smaller 22-gauge Tuohy needle is not available in the UK, we have no personal experience in its use, although it seems a sensible option. We would advise using the size of needle to which one is most accustomed. In common with the majority of anaesthetists in this country, we use the 16-gauge needle for all of our adult epidural work and feel more comfortable with the tactile feedback from these larger needles.

We read with interest the described technique for performing breast surgery using a paravertebral block with sedation. It would appear that up to six separate injections are being made in each patient to achieve an adequate surgical block from T1 to T6. We would question the wisdom of multiple injections given that even in expert hands there is a risk of complications with each pass of the needle It is well documented that there is a good spread across several dermatomes after a single paravertebral injection. We are currently conducting a clinical study which involves injecting methylene blue-labelled bupivacaine paravertebrally before open thoracotomy. In our experience to date, it is not uncommon to see spread over 4–6 intercostal spaces after an injected volume of 0.5% bupivicaine 20–30 ml. These as yet unpublished findings concur with previously published data, both clinically[1] and in radiological studies.[6] It would seem unnecessarily risky to perform multiple injections when one or perhaps two would adequately suffice.

P W. Thomas
D J Sanders
R. G Berrisford
Royal Devon and Exeter Hospital
Devon, UK

1 Richardson J, Sabanathan S. Thoracic paravertebral analgesia. *Acta Anaesthesiol Scand* 1995; **39**. 1005–15
2 Richardson J, Lonqvist PA. Thoracic paravertebral block. *Br J Anaesth* 1998, **81**: 230–8
3 Pusch F, Freitag H, Weinstabl C, Obwegeser R, Huber E, Wilding E. Single injection paravertebral block compared to general anaesthesia in breast surgery. *Acta Anaesthesiol Scand* 1999; **43**: 770–4
4 Richardson J, Cheema SPS, Hawkins J, Sabanathan S. Thoracic paravertebral space location. *Anaesthesia* 1996; **51**: 137–9
5 Lonnqvist PA, MacKenzie J, Soni AK, Conacher ID. Paravertebral blockade, failure rate and complications. *Anaesthesia* 1995, **50**. 813–15
6 Conacher ID, Kokri M. Postoperative paravertebral blocks for thoracic surgery A radiological appraisal. *Br J Anaesth* 1987; **59**: 155–61

Complications of paravertebral block

Editor,—We read with interest the case report of Thomas, Sanders and Berrisford on pulmonary haemorrhage after percutaneous paravertebral block.[1] It is well recognized that in patients who have undergone previous thoracic surgery, the paravertebral space may be fibrosed and that this can interfere with the appreciation of loss of resistance.[2] In such cases, it is important to locate the transverse process to prevent the Tuohy needle from penetrating too deeply.

The authors do not mention whether in this patient the transverse process was identified. It is imperative that this bony landmark be located without the needle penetrating any deeper than necessary. If the transverse process is not contacted initially at a depth of approximately 3 cm, the needle should be withdrawn and reinserted in either a caudal or cephalad direction.[3] From the displayed CT scan, the approximate position of the transverse process can be measured at a depth of 3 cm. The Tuohy needle was noted to be at a depth of 6 cm when blood was aspirated, so we assume that the authors failed to identify the transverse process. The Tuohy needle must have breached the pleura and entered the lung tissue. The most likely source of the pulmonary haemorrhage seen on bronchoscopy would be from a traumatized pulmonary vessel.

Our second point relates to the single axial CT slice of the chest. The left paravertebral space may be 5–15 mm wide in the normal subject.[4] Using the scale displayed on the CT image, the left paravertebral space is approximately 5 mm wide and within normal limits. Further interpretation of the paravertebral region to identify abnormal tissue attenuation material within the normal fatty space is prevented by the position of the author's marker and the window settings chosen to display the image. A paravertebral haematoma may have been visible on other slices in the examination series but in our opinion the displayed image fails to show this condition.

S. S. Wyatt
Department of Anaesthesia
Sir Charles Gairdner Hospital
Perth, Western Australia
R. A. Price
Department of Diagnostic Radiology
Royal Perth Hospital
Perth, Western Australia

1 Thomas PW, Sanders DJ, Berrisford RG. Pulmonary haemorrhage after percutaneous paravertebral block. *Br J Anaesth* 1999; **83**: 668–9
2 Richardson J, Lonnqvist PA. Thoracic paravertebral block. *Br J Anaesth* 1998; **81**: 230–8
3 Kopacz DJ, Thompson GE. Celiac and hypogastric plexus, intercostal, interpleural, and peripheral neural blockade of the thorax and abdomen. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockage*, 3rd Edn. Philadelphia: Lippincott–Raven, 1998; 451–89
4 Gupta SK, Mohan V. The thoracic paraspinal line: further significance. *Clin Radiol* 1979; **30**: 329–35

British Journal of Anaesthesia 84 (3): 425–7 (2000)

Book Reviews

Anesthesiologist's Manual of Surgical Procedures, 2nd Edn. R. A. Jaffe and S. I. Samuels (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 1084; indexed; illustrated. Price $US90.00.

This textbook is written almost entirely by the staff of Stanford University School of Medicine. It contains a description of surgical procedures and their anaesthetic needs. Imagine that you are scheduled to anaesthetize a patient for a surgical procedure with which you are unfamiliar or of which you have had no practical experience, what do you do? You can either ask a colleague or search the literature for relevant articles that describe the anaesthetic requirements for the particular procedure; in all likelihood, this is time-consuming and often unsuccessful. This textbook was designed specifically to fill in that 'gap'.

The format is unique: the book is divided into 13 chapters representing the major surgical specialties and each chapter is subdivided into surgical procedures. Each procedure is described by a surgical expert who gives a brief description of the procedure and a summary of the factors that may be of particular interest for the anaesthetist, such as patient positioning, common complications, special needs and expected duration of surgery (which to me seems a bit longer than in the UK). Furthermore, there is a brief description of the patient population characteristics. The surgeon's viewpoint is followed by the anaesthetic considerations written by an 'anaesthesiologist' with special expertise in providing anaesthesia to patients undergoing the particular surgery being described. These anaesthetic considerations are detailed, and rather than rigidly describing a specific recipe which can vary among anaesthetists, a technique that works for that procedure is outlined together with the suggested monitoring modalities, the most common perioperative complications to be expected and the practicalities of postoperative pain management. The experience and sound clinical judgement of the authors can indeed enhance the formulation of an anaesthetic plan.

At the end of this massive textbook, there are appendices containing pertinent and up to date information for the anaesthetist, such as: preoperative laboratory testing and diagnostic studies; considerations for latex allergy; and a comprehensive chapter on drug interactions (with a section on herbal remedies which are increasingly being used by our patients).

Despite the fact that this book is US-based, most of the chapters are also of relevance to the British anaesthetist. The book is comprehensively illustrated with anatomical diagrams. It is concise and well written, except for the excessive use of abbreviations, medical symbols and telegraphic sentence structure, which I found annoying.

For me, this textbook is a superb aid for the 'harried' anaesthetist confronted with unfamiliar surgical procedures on patients whose preoperative visit can only take place a few hours before scheduled surgery (an increasing trend in our hospital). Furthermore, it is well referenced and, despite its 'Americanisms' should be a useful addition to any departmental library. I know what I will do next time I am assigned to produce anaesthesia for a patient undergoing a procedure I am not familiar with!

B. Appadu

Fundamentals of Anaesthesia. C. Pinnock, T. Lin, T. Smith and R. Jones (editors). Published by Greenwich Medical Media, London. Pp. 867; indexed; illustrated. Price £55.00

To launch a new textbook of anaesthesia onto a market already well supplied requires considerable courage, by both the authors and more particularly by the publisher. Those preparing for the primary FRCA can choose between familiar books that have evolved through many editions with a pedigree going back more than 50 yr to more recent large format paperbacks which have rapidly established their position as good guides for the fledgling anaesthetist. What then can this new *Fundamentals of Anaesthesia* offer to challenge the entrenched opposition?

In format it is another large paperback, and it is a weighty volume Carrying it around so that it can be used in those many idle moments created by the delays that punctuate the modern surgical list, would require tenacity. But the layout is clear with good line drawings and the use of shaded text boxes to highlight lists and other key points as an aid to learning. The preface explains that the publication of a defined syllabus for the primary FRCA provided the impetus to bring together a group of authors, mostly from the Midlands of England, to write a text based on that syllabus. In that the syllabus also guides and constrains the examiners, this may appear a sensible premise. Reading the book with the syllabus alongside, it is very obvious how closely the approach has been followed. However, the trainee who believes that as a consequence of this approach every aspect is covered needs to be cautious. The OSCE (objectively structured clinical examination), an important element of the primary FRCA, covers many areas that cannot be condensed into a textbook More pertinently, the text sometimes runs out before providing complete coverage. For example, under anatomy, the syllabus clearly lists 'sacral and coccygeal plexuses, nerves of the leg', but although the sacral plexus is described in the chapter on anatomy and femoral nerve block in that on regional anaesthesia and analgesia, this is the limit of the coverage. Similarly, the syllabus lists the 'eye and orbit', and the structure of the eye is well described but not the orbit. As an examiner who has watched the look of panic assailing the faces of good candidates when asked the set questions on nerve blocks at the ankle or the structures passing into the orbit, it is clear that they will not find salvation here.

Physics and clinical measurement have, as in the past, become an increasingly important part of the primary FRCA. For coverage of basic physics, the editors have turned to a physicist rather than an anaesthetist. The result is that concepts are rarely illustrated by directly linking examples from anaesthesia; this makes for a dry approach. There is coverage of basic calculus which, although not totally irrelevant to anaesthesia, is not referred to in the syllabus; its presence here will only serve to heighten anxiety in the already stressed candidate. A more fundamental failure is the information relating to critical temperature, a topic of perennial interest in the primary FRCA and mentioned specifically in the syllabus. There is no reference in the index and scrutiny of the text eventually revealed only brief coverage in a paragraph headed 'boiling point'. Here, critical temperature for a gas is defined as 'the temperature *at which* no amount of increased pressure will cause it to liquefy'. This appears to indicate confusion over critical temperature and critical pressure that, were it to come from an examinee, would place them in some jeopardy.

There is much that is well done. The succinct coverage of intraoperative management and resuscitation would be of value to any senior house officer. The excellent chapter on cardiac physiology and many of the 16 chapters on pharmacology written by Tim Smith, one of the editors, provide good overviews but similar coverage is available elsewhere.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

In setting out to link themselves directly to the syllabus, the editors have defined a new approach but it may be too simplistic. For the candidate, it is the weighting of different topics by the examiners that is important. To be wrong on an obscure point may not matter; to be wrong on a basic one may be irrecoverable. New approaches in textbooks for this crucial market are always to be welcomed but this approach does not seem to provide the solution.

S. Ingram

Obstetric Anesthesia, 2nd Edn. M. Norris (editor) Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 845; indexed; illustrated Price US$125.00.

I like to have a number of obstetric texts on my shelf, and I bought the first edition of Mark Norris' book out of curiosity alone. The style of presentation with text boxes, tables, charts and photographs to support the text made it attractive to read. The quality of much of the writing made it a frequent first choice when information was required, and the binding rapidly gave way under the strain. The new edition appears to have been assembled at greater expense. In the preface, the editor lays out the organization of the book according to 'the way an anesthesiologist approaches a patient'. While the headings of the sections match the aim, the content of the various sections are not comprehensive and do not always seem to belong. This does not seem to matter too much because the index seems to work well, and this book is not going to be read from cover to cover. The approach is generally clinical. I could not find a chapter on pharmacology of local anaesthetics, but some information is available in the chapters dealing with perinatal pharmacology and neuroaxial drugs. The chapters are well referenced and the ones I selected at random had been updated to include articles from 1997.

The book is unashamedly American, with a section on the organization of an anaesthesia/analgesia service, and an appendix with several ASA standards and guidelines quoted verbatim. The relevance of some of this to British practice is remote, but the concepts are definitely applicable. It is a pity that these sections are not rewritten in a European edition. The authors are almost exclusively American, but there is a South African perspective. My personal favourites are the chapters dealing with intrathecal drugs and haematological disease. The latter gives a good account of thromboelastography. I am dismayed that the recommendations for epidural and intrathecal anaesthesia for Caesarean section do not make it clear that abolition of touch to T5 is required. Giventhat this is the commonest source of related litigation, the experts should give clear guidance on how blocks should be tested.

No book is perfect, but I like this one. It is friendly and informative and rewards consultation. I would not advise British trainees to buy it, but somebody else should do it for them. I had already placed my order before I was asked to write this review. I hope it holds together longer than the first edition.

G. Lyons

Peripheral Nerve Block: a Color Atlas. J. E. Chelly (editor) Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 223; indexed; illustrated. Price $US95.00

This multi-author colour atlas is an ambitious work and is almost unique in its focus, concentrating solely on peripheral nerve block (other regional anaesthesia atlases invariably include central neural blocks as a major component). No book of this nature is truly comprehensive as editors and authors tend to concentrate on the regional anaesthetic techniques with which they are most familiar. Nevertheless, there are 29 discrete nerve blocks described for adults with a further 10 techniques in a section devoted to paediatric peripheral nerve blocks. Unusually, there is considerable emphasis on inserting perineural catheters for continuous nerve blocks with 12 techniques described in a separate section. The editor is French, as are 18 of the 30 authors, hence the frequent use of French language references in the text. In addition to editing the book, Dr Chelly has written 16 of the 49 contributions to the book, which has ensured editorial consistency and a definite, although rather idiosyncratic, literary style to the book. A number of terms such as 'truncular', 'sus-aponeurotic', 'rear' (rather than posterior) are presumably literal translations from the original French text.

A colour atlas should be well laid out, visually attractive and of good quality to encourage the reader to explore its contents and to justify the often expensive purchase price. There is a lot of commonsense advice in this book, which is well produced on high quality paper, with strong hardback covers and binding and an attractive front cover design. However, some of the colour photographs and figures are of poor quality and tend to detract from the value of the text. The computer-generated labels on many of the pictures are sometimes uninformative and even misleading. especially in the brachial plexus pictures. Several photographs have clearly been downloaded directly from digital imaging systems with obvious pixellation that also detracts from the overall quality of the illustrations.

The book is divided into four sections. The first is on general concepts and is a very brief summary of patient care, equipment, local anaesthetic and adjuvant drug pharmacology. It is too brief to be of any real value, especially as it suggests that pilocarpine (prilocaine?) is a local anaesthetic. Section two on single-shot blocks is the largest section and concentrates primarily on upper and lower limb blocks; only eight of the techniques described relate to the head and neck and trunk, and there is no description of ilioinguinal field, penile, rectus sheath or lumbar paravertebral techniques. Similarly, in section 3, continuous catheter infusions are limited to techniques of the upper and lower limbs, with no mention of intercostal, paravertebral or interpleural catheters. Section 4 is devoted to paediatric blocks and again concentrates on limb blocks but does include penile and ilioinguinal blocks.

There are no major errors of fact in any of the techniques described although, as with any regional anaesthesia textbook, there is room for disagreement about the practical details of several techniques and the value of one or two more is questionable (continuous catheter techniques at the wrist for instance). Most techniques are described simply, clearly and with useful practical tips to increase the chances of a successful outcome. The perineural catheter section is particularly useful as these techniques are rarely covered by other textbooks in any detail. In general, this atlas succeeds in its purpose which is to encourage a reader, unfamiliar with a block technique, to perform it with more confidence having read the description. An inexperienced practitioner, however, may be disappointed by the relatively restricted number of peripheral blocks described.

H. B. J. Fischer

Handbook of Neuroanaesthesia. P. Newfield and J. E. Cottrell (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 431; indexed. Price $US39.95.

This is a pocket-sized book which covers the various aspects of neuroanaesthesia comprehensively. It is broadly divided into three categories: 'general considerations' which include the brain and spinal cord physiology and metabolism, neurophysiologic monitoring, cerebral protection, preoperative evaluation and perioperative pain management; 'anaesthetic management' for head trauma, supratentorial and posterior fossa tumours, aneurysms, neurendocrine procedures, epilepsy, spinal cord surgery and neurosurgery in paediatric and pregnant patients; and 'intensive care', including respiratory and cardiovascular care, fluid management and nutritional support. Each chapter is well set out and the bold type headings make it both easy to read and simple to find specific topics of interest. We liked the wide margin which provides space to add one's own notes or comments.

There is a certain American bias, particularly on preoperative cardiovascular investigations and the use of pulmonary artery catheters. Also, early surgery for all aneurysms is recommended, regardless of grade, which is not well supported by evidence.

L.B. (a trainee) found the content excellent with good attention to detail, particularly in the sections on physiology and pharmacology. The graphs and tables are clear and reinforce the written information. The approach to spinal x-rays is well done and can be applied simply. This comprehensive handbook provides useful information on a practical day-to-day basis and for a candidate taking the FRCA.

L.B. would have liked more details on ventriculo-peritoneal shunts in adults. This is a frequently performed operation, often on unstable patients as an emergency; therefore, patients are sometimes operated on by trainees. A simple explanation of the procedure itself and a brief summary of the potential problems would have been useful. Also, with regard to surgery for scoliosis (often involving paediatric patients), little mention is made of postoperative care such as the necessity for a HDU/ICU bed or the possibility of postoperative ventilation.

The index is fairly extensive and user-friendly. On looking up the anaesthetic management of supratentorial tumours and draining of a subdural haematoma (the patients on my last neurosurgical list), the information provided was well set out, with particular problems highlighted, and was suitably specific to enable me to anaesthetize the patient adequately.

Sections that L.B. thought were excellent include: 'the anaesthetic management of head trauma', which is vital to patient outcome and is an area where anaesthetic input can make a significant difference; the inclusion of a chapter on 'neurosurgery in the pregnant patient' as pregnancy provides unique problems of its own; 'diagnostic neuroradiology' as this is assuming an increasingly important role and will no doubt become even more significant in the future; and finally, 'intensive care'. L.B. found this a well set out and comprehensive account of neuroanaesthesia and thoroughly recommends it.

R.S. (a consultant) looked for ways to modify his own practice. Is it safe or appropriate to use the internal jugular vein for CVP monitoring in neurosurgical patients? You will not find the answer in this book! Is i.v. anaesthesia really better than an inhalation technique for craniotomy? Is the cerebroprotective effect of isoflurane clinically important? Again, the text stays on the fence and does not offer any kind of overview. What (in detail) should we do about arterial pressure control during neurovascular surgery? Again, no sign of a recipe or practice guidance.

This is a worthwhile purchase both for the individual trainee, either preparing for examinations or alternatively for use on a practical daily basis, or for an anaesthetic department. Consultants may prefer something more comprehensive and questioning.

L. Barker
J. R. Sneyd

Understanding Anesthesia Equipment. J. A. Dorsch and S. E. Dorsch. Published by Wilkins, Baltimore. Pp. 1066; indexed; illustrated. Price $US95.00.

Several changes have been made to the content of this volume since it was first published in 1975 and last updated in 1994, but it still retains a very 'dated' feel. The shiny paper, grainy, often poor quality, black and white photographs and layout do not make for easy reading. The text resembles the examination answers of an extremely knowledgeable candidate, with short, clipped sentences and paragraphs, and multiple headings and sub-headings. Every last fact available is presented but often with no guidance as to their relative importance. For example, inadvertent oesophageal intubation is covered in 3½ pages with no less than 24 separate tests being described, but without any indication as to which should be preferred.

The quantity of information offered is frequently imbalanced, two pages being devoted to the technique of laryngoscopy while 17 are spent in descriptions of every laryngoscope blade ever produced. This book is intended for trainee anaesthetists and nurse anaesthetists. One therefore looks for clear, simple guidelines for managing equipment malfunction. For example, if the laryngoscope fails; tighten or change the bulb, check the electrical connection between blade and handle, check and replace the batteries. Several of these faults are mentioned in the text but not gathered together in any coherent form.

A major feature of this book is the exhaustive list of references which follow each chapter, for example 1280 are cited for the chapter on tracheal tubes, 558 on largyngeal mask airways (50% of all references on the LMA found in a literature search!) and 508 on oximetry. In the latter case, the text occupies 20 pages and the references a further 14. Regrettably, the large number of references does not always add to understanding Twenty-one references are used to support the statement that oximeters are inaccurate when Sp_{O_2} is low, a well established point that is made clear in the manufacturer's literature. In contrast, the description of the principles of oximetry occupies less than a page and is cursory, no mention being made of the means by which the displayed value is averaged, an important factor in the accuracy and reliability of the instruments.

Practical tips are sometimes given in great detail, for example the use of a steadying foot when changing an oxygen cylinder, but are sometimes hidden among theoretical information or omitted altogether. Some are misleading and arise from a poor grasp of the underlying principles. For example, supramaximal peripheral nerve stimulation requires that an adequate current density be achieved in the nerve. Large surface electrodes, such as ECG electrodes, allow a large total current to flow but often an inadequate current density Small, carefully placed electrodes are thus essential. These points are made in the text but their relevance is not made clear and the accompanying photographs show ECG electrodes being used.

There are several notable omissions from the list of equipment covered, especially transfusion equipment and patient warming devices. It could be argued that these are not central to 'anaesthesia' but as items of equipment in regular use in the operating theatre their function and use are important for anaesthetists. In contrast, changes in product liability legislation have largely excluded the anaesthetist from the care and maintenance of anaesthetic equipment. While anaesthetists should have an understanding of how their equipment works, they do not need the detailed knowledge to dissemble and repair that was necessary even 25 yrs ago. Thus much of the information in the opening chapters is redundant.

If this book is to fulfil the promise of its title, a complete overhaul is needed for any subsequent editions; it cannot be recommended in its present form.

C. D. Hanning

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5\text{–}7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; **59**: 14–23

Chapter in a book:

2. Hull CJ. Opioid infusions for the management of postoperative pain In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985; 155–79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn Springfield, Illinois: Charles C. Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly

numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131–7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

The *British Journal of Anaesthesia* has implemented a change in reference style. We retain the Vancouver style, but the journal name is now abbreviated, only the change in the last page number is given and no full stop ends the reference (i.e. *Br J Anaesth* 1998; **81**: 232–9)

12th World Congress of Anaesthesiologists
Montréal, Canada • June 4 - 9, 2000

millennium

To receive registration information for this important world congress,
please contact the Congress Secretariat
c/o Events International Meeting Planners Inc.
759 Victoria Square, Suite 300, Montréal, Québec, Canada H2Y 2J7
Tel.: (514) 286-0855, Fax: (514) 288-7945, E-mail: info@eventsintl.com or visit our Web site: http//www.wca2000.com

BJA

International Journal of Anaesthesia

Volume 84 Number 4 April 2000

EDITORIALS

429 I: Hot air or full steam ahead? An empirical pharmacokinetic model of potent inhalational agents
T. Bouillon and S. L. Shafer

432 II: Assessment of clinical competence
D. I. Newble

434 III: 2000 – Time to apply Occam's razor to failure of hypoxic pulmonary vasoconstriction during one lung ventilation
I. D. Conacher

CLINICAL INVESTIGATIONS

437 Pharmacokinetics of inhaled anaesthetics in a clinical setting: description of a novel method based on routine monitoring data
S. Rietbrock, H. Wissing, I. Kuhn and U. Fuhr

443 Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane
H. Wissing, I. Kuhn, S. Rietbrock and U. Fuhr

450 General *versus* regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials
S. C. Urwin, M. J. Parker and R. Griffiths

456 Novel bioadhesive delivery system for percutaneous local anaesthesia
D. F. McCafferty, A. D. Woolfson and G. P. Moss

459 Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery
J. J. Wang, S. T. Ho, H. S. Liu and C. M. Ho

463 Acupressure and prevention of nausea and vomiting during and after spinal anaesthesia for Caesarean section
D. Harmon, M. Ryan, A. Kelly and M. Bowen

LABORATORY INVESTIGATION

468 Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage
V. Krejci, L. Hiltebrand, A. Banic, D. Erni, A. M. Wheatley and G. H. Sigurdsson

REVIEW ARTICLE

476 P2X receptors in sensory neurones
G. Burnstock

SHORT COMMUNICATIONS

489 Randomized placebo-controlled trial to assess the effect of remifentanil and propofol on bispectral index and sedation
A. N. Strachan and N. D. Edwards

491 Role of dominant hand position during external cardiac compression
P. Kundra, S. Dey and M. Ravishankar

494 Epidural top-up solutions for emergency Caesarean section: a comparison of preparation times
D. N. Lucas, P. J. Borra and S. M. Yentis

497 *In vitro* validation of gastric air tonometry using perfluorocarbon FC 43 and 0.9% sodium chloride
J. Graf, B. Königs, K. Mottaghy and U. Janssens

CASE REPORTS

500 Malignant hyperthermia in infancy and identification of a novel RYR1 mutation
D. Chamley, N. A. Pollock, K. M. Stowell and R. L. Brown

505 Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment
A. Patel, E. Harrison, A. Durward and I. A. Murdoch

508 Monitoring equipment induced tachycardia in patients with minute ventilation rate-responsive pacemakers
P. A. Southorn, G. S. Kamath, G. M. Vasdev and D. L. Hayes

510 Stunned myocardium after hip arthroplasty
M. Mizogami, K. Shimo, T. Taguchi and Y. Horita

514 Spinal cord infarction and tetraplegia — rare complications of meningococcal meningitis
R. O'Farrell, J. Thornton, P. Brennan, F. Brett and A. J. Cunningham

518 Cranial subdural haematoma associated with dural puncture in labour
D. J. A. Vaughan, C. A. Stirrup and P. N. Robinson

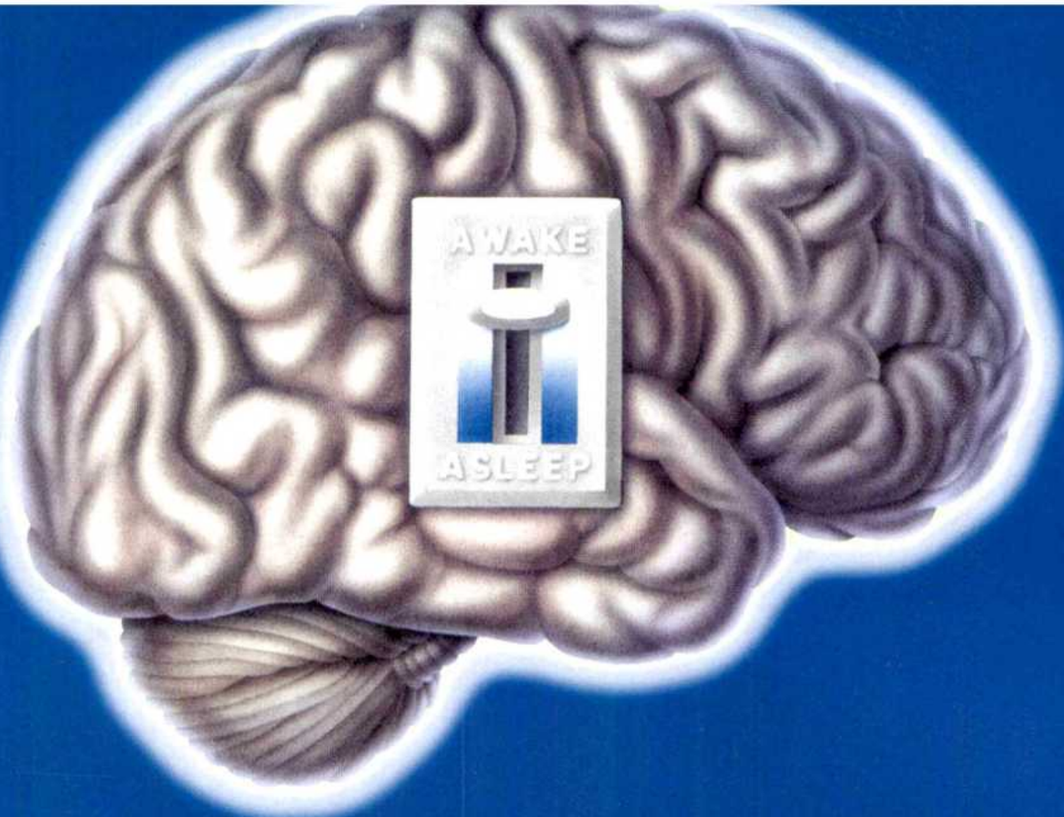
521 Delayed bilateral internal carotid artery thrombosis following accidental strangulation
S. H. Kiani and D. C. Simes

COMMENTARY

525 Watching anaesthetists work: using the professional judgement of consultants to assess the developing clinical competence of trainees
J. D. Greaves and J. Grant

534 CORRESPONDENCE

541 BOOK REVIEWS



The First Direct Measure of Anaesthetic Effect.

The Bispectral® (BIS®)

is a processed EEG parameter that directly measures the hypnotic effects of anaesthetic and sedative agents on the brain.

Clinically Proven -

titration of anaesthetic agent using the BIS results in:

- *Decreased drug usage*[1,3]
- *Faster and more predictable wake-up times*[2]
- *Improved quality of recovery*[2]
- *Reduced PONV*[6]
- *Faster eligibility for discharge from Recovery*[2,3]
- *Means of detecting unexpected patient arousal*[5]

** 1-6 References on file at Aspect Medical Systems*

To learn more about BIS, contact us:

Aspect Medical Systems
International B.V.
Haagse Schouwweg 8b
2332 KG Leiden
The Netherlands

Tel.nr. +31.71.5725935
Fax nr. +31.71.5725936

Web: www.aspectms.com
E-mail: amsint@aspectms.com

ASPECT® MEDICAL SYSTEMS

BIS® by Aspect

Aspect, BIS, the BIS logo and Bispectral Index are registered trademarks of Aspect Medical Systems, Inc.

Editorial Board

Editor-in-Chief

JENNIFER M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Senior Lecturer in Anaesthesia, *University of Leeds*
D. G. LAMBERT, Senior Lecturer in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. R. ELLIS, Professor of Anaesthesia, *University of Leeds*
W. FITCH, Professor of Anaesthesia, *University of Glasgow*
G. M. HALL, Professor of Anaesthesia, *University of London*
D. J. HATCH, Portex Professor of Anaesthesia, *University of London*
P. HUTTON, Vice-president, *Royal College of Anaesthetists*
R. D. MILLER, Professor of Anesthesia, *University of California, San Francisco*
I. POWER, Associate Professor, *University of Sydney, Australia*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. SEAR, Clinical Reader in Anaesthesia, *University of Oxford*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Professor of Anaesthesia, *University of Plymouth*
L. STRUNIN, President, *Royal College of Anaesthetists*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Production Staff

E. GOODING, Senior Production Editor, *Oxford University Press*
C. DUNNE, Editorial Assistant, *Oxford University Press*

Please visit the Journals's World Wide Web site at http://bjanaes.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to BJA comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate

Institutions: UK and Europe £217, Rest of World US$346
Trainees: UK and Europe £105, Rest of World US$168
Single issue: UK and Europe £23, Rest of World US$36

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express, Diners, JCB); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; Email: jnl.info@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 80 onwards to* Oxford University Press. *For Vols 1–79* to Dawsons Back Issues, Cannon House, Folkestone, Kent. Tel: +44 (0)1303 203612; Fax +44 (0)1303 203617.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262.

© *The Board of Management and Trustees of the British Journal of Anaesthesia* 2000

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$346. British Journal of Anaesthesia is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

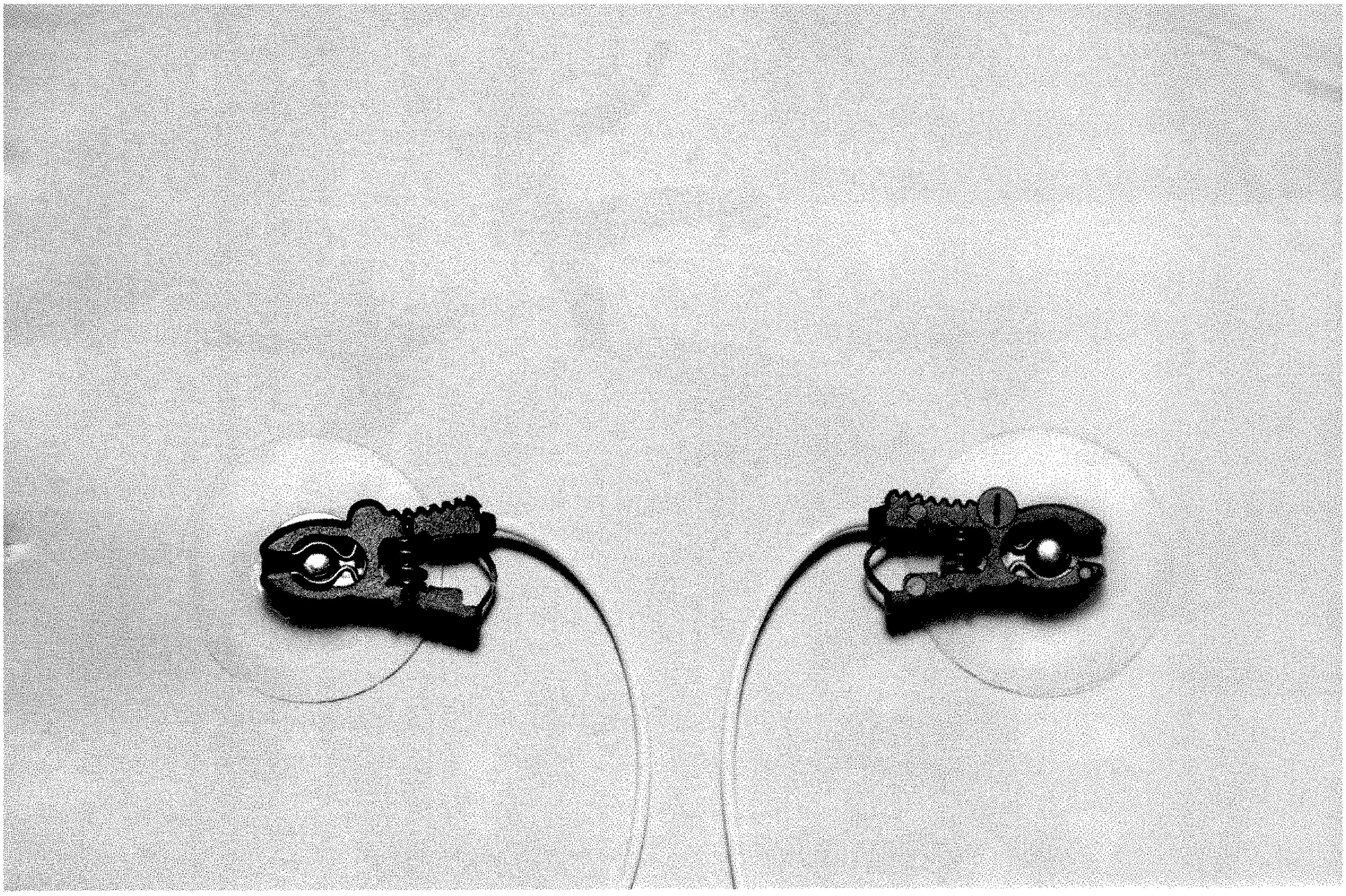
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

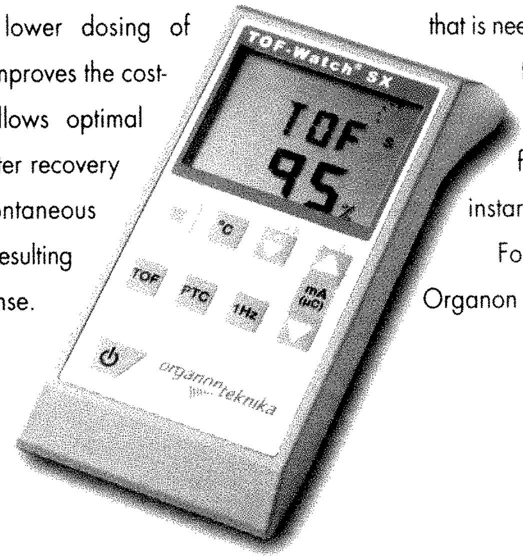


Eyes that never miss a twitch.

Monitoring neuromuscular block in the ICU makes sense.

Monitoring muscular block in the intensive care has clear benefits for both patients and staff.

The TOF-Watch contributes to lower dosing of NMBAs, enhances patient safety and improves the cost-effectiveness of treatment. It also allows optimal control of depth of block, promotes faster recovery of neuromuscular function and spontaneous ventilation, and helps avoid dysfunction resulting from prolonged paralysis. It makes sense.



TOF-Watch devices are small, lightweight and easy to operate. Calibration and selection of the desired stimulation mode are all that is needed. Continuous monitoring and data display are fully automatic.

The TOF-Watch range offers different models for specific applications. The TOF-Watch S, for instance, is ideally suited for daily ICU practice.

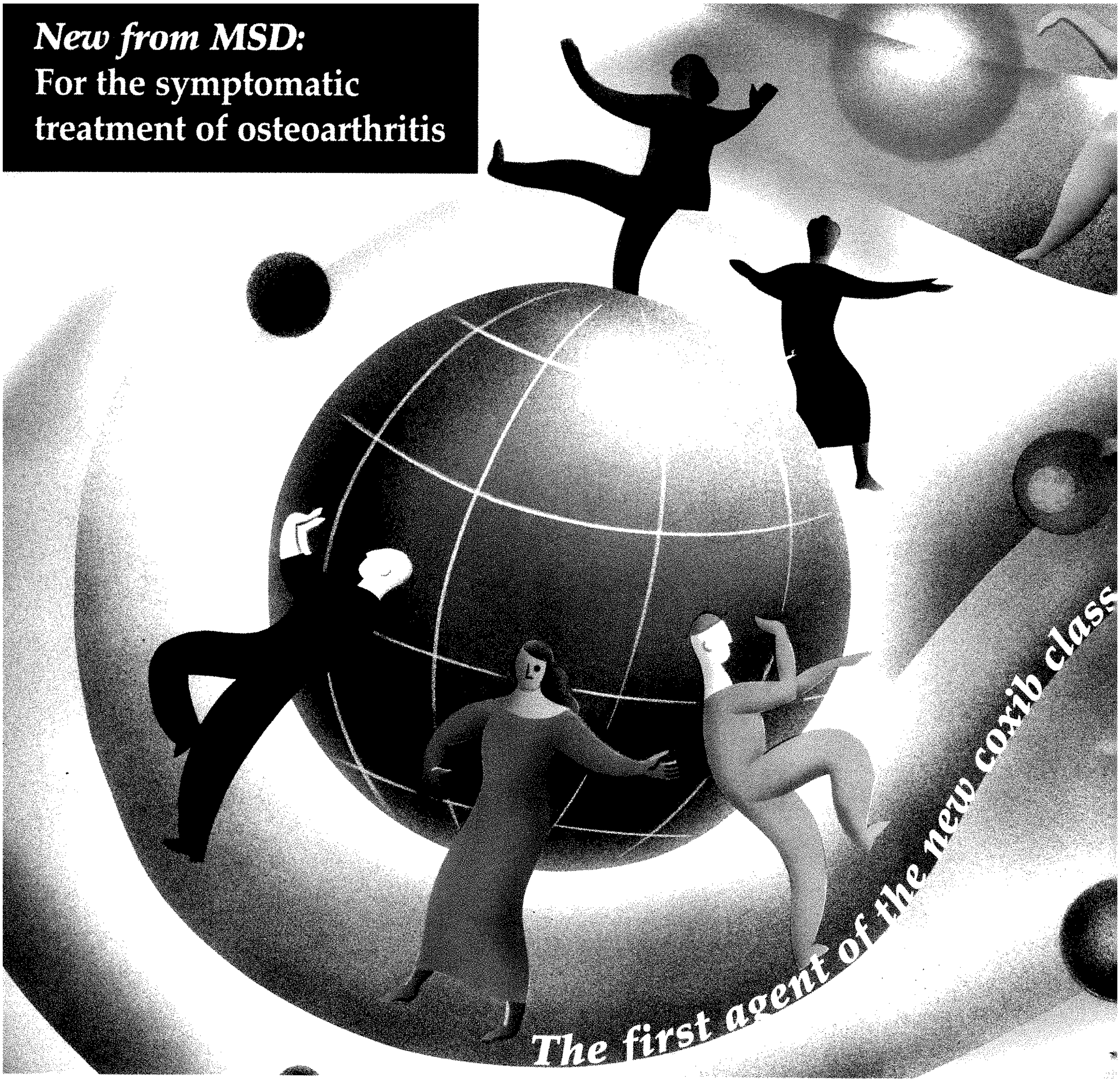
For further details, please contact your local Organon Teknika representative.

organon teknika

TOF-Watch®

safe NMBA use pays dividends

For more information: Organon Teknika bv, Boseind 15, 5281 RM Boxtel, telephone +31 (0)411 654911, telefax +31 (0)411 654201 Internet: http://www.organonteknika.com


New from MSD:
For the symptomatic treatment of osteoarthritis
The first agent of the new coxib class

VIOXX®▼
(rofecoxib)
ABRIDGED PRODUCT INFORMATION

Refer to Summary of Product Characteristics before prescribing

PRESENTATION

VIOXX Tablets: 12.5 mg and 25 mg tablets each containing 12.5 mg or 25 mg of rofecoxib.

VIOXX Oral Suspension: 12.5 mg/5 ml and 25 mg/5 ml, each 5 ml oral suspension containing either 12.5 mg or 25 mg of rofecoxib.

USES

Symptomatic relief in the treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION

The adult starting dose is 12.5 mg once-daily orally with or without food. Some patients may receive additional benefit by increasing the dose to 25 mg once-daily. 25 mg daily should not be exceeded.

Elderly: Exercise care when increasing the dose from 12.5 mg to 25 mg.

Hepatic insufficiency: In mild hepatic insufficiency, do not exceed 12.5 mg once-daily.

Children: Not recommended.

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Moderate or severe hepatic dysfunction (Child-Pugh score ≥7). Estimated creatinine clearance <30 ml/min. Patients who have developed asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Third trimester of pregnancy and lactation. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis.

Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with rofecoxib.

Consider the possibility of fluid retention and exercise caution when rofecoxib is used in patients with pre-existing oedema, a history of heart failure, left ventricular dysfunction or hypertension.

Maintain appropriate supervision when treating the elderly or patients with renal, hepatic or cardiac dysfunction with rofecoxib.

In clinical studies, some osteoarthritis (OA) patients treated with rofecoxib developed perforations, ulcers or bleeds (PUBs). Patients with a prior history of a PUB and patients greater than 65 years of age appeared to be at a higher risk for a PUB.

At daily doses higher than 25 mg, the risks of gastro-intestinal symptoms, oedema or hypertension are increased.

Elevations of ALT and/or AST (≥3 times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with rofecoxib.

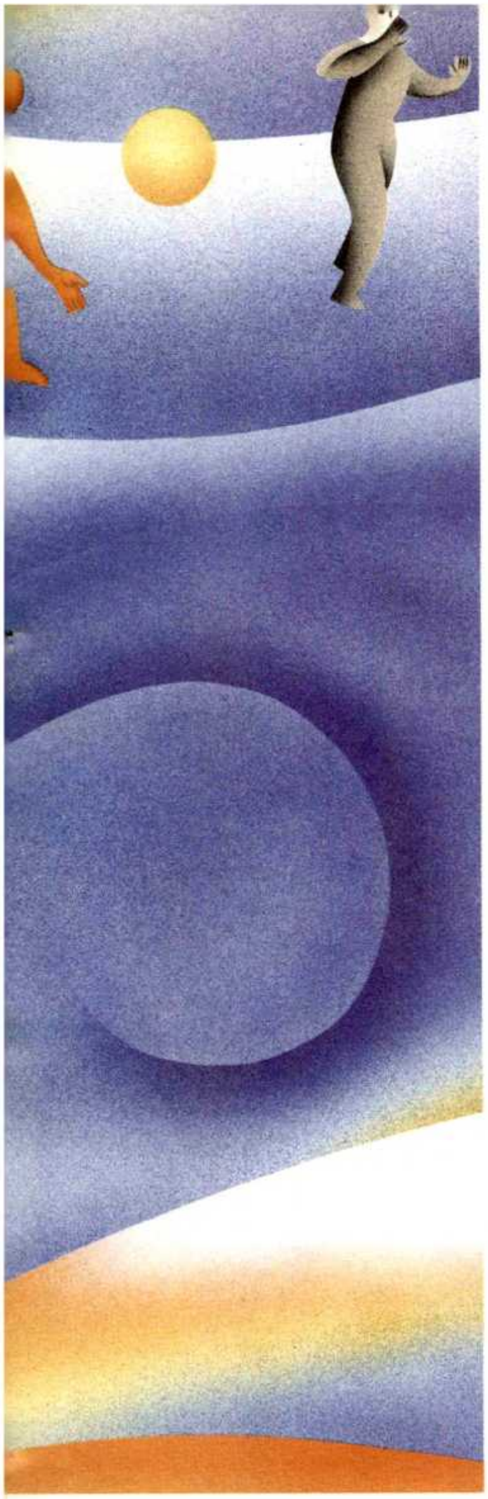
Any patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, discontinue rofecoxib.

Rofecoxib may mask fever.

Use of rofecoxib is not recommended in women attempting to conceive.

Interactions (pharmacodynamic): Warfarin: closely monitor the prothrombin time when therapy with rofecoxib is initiated in patients on warfarin therapy. *ACE-inhibitors:* administration of 25 mg daily of rofecoxib with benazepril, 10 mg to 40 mg daily for four weeks to patients with hypertension was associated with a small attenuation of the antihypertensive effect compared to the ACE inhibitor alone.This should be considered in patients taking rofecoxib concomitantly with ACE inhibitors. *Beta-blockers and diuretics:* concomitant use of NSAIDS may reduce the antihypertensive efficacy of beta-blockers and diuretics and the other effects of diuretics. *Aspirin:* at steady state, rofecoxib 50 mg once-daily had no effect on the anti-platelet activity of low-dose (81 mg once-daily) aspirin. Avoid concomitant administration of rofecoxib with higher doses of aspirin or other NSAIDS. *Cyclosporin/tacrolimus:* monitor renal function when rofecoxib and either cyclosporin or tacrolimus is used in combination.

Interactions (pharmacokinetic): Lithium: NSAIDS may increase plasma lithium concentrations. *Methotrexate:* consider adequate monitoring for methotrexate-related toxicity when rofecoxib and methotrexate are administered concomitantly. *CYP1A2 substrates:* exercise care with concomitant administration of rofecoxib with drugs primarily metabolised by CYP1A2 (e.g. theophylline, amitriptyline, tacrine and zileuton). *Midazolam:* a modest 30% reduction of the AUC of midazolam was seen with rofecoxib 25 mg daily, most likely due to increased first pass metabolism through induction of intestinal CYP3A4 activity by rofecoxib. *CYP3A4 substrates:* in spite of a modest induction of intestinal CYP3A4 activity, the pharmacokinetics of drugs metabolised primarily by CYP3A4 are not expected to be affected to a clinically significant extent. However exercise care when co-prescribing substrates of CYP3A4 with rofecoxib. *Rifampicin:* co-administration of



In clinical studies: inhibits COX-2 but not COX-1[1*]

- The power of high-dose NSAIDs – diclofenac and ibuprofen.[2]
- Superior GI safety profile compared to conventional NSAIDs – diclofenac, ibuprofen and nabumetone.[2, 3]
- True once-daily therapy – for a wide range of patients.[2]

* statistically significant inhibition of COX-1 has not been documented with any dose of VIOXX given to humans.

TRUE ONCE-DAILY

NEW

VIOXX® ▼

(rofecoxib)

Selective. Strong. Simple.

rofecoxib with rifampicin, a potent inducer of CYP enzymes, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, consider the use of the 25 mg dose when rofecoxib is used with potent inducers of hepatic metabolism.

Based on *in vitro* data, rofecoxib is not expected to inhibit cytochromes P450, 2C9, 2C19, 2D6 or 2E1.

Pregnancy: Do not use in the last trimester of pregnancy, because like other prostaglandin synthesis inhibitors rofecoxib may cause uterine inertia and premature closure of the ductus arteriosus. Rofecoxib should not be used during the first two trimesters of pregnancy unless the benefit to the patient outweighs the risk to the foetus.

Lactation: contra-indicated.

SIDE EFFECTS

The following drug-related undesirable effects were reported at an incidence greater than placebo in clinical studies in patients treated with rofecoxib 12.5 mg or 25 mg for up to six months.

Common (>1/100, <1/10)

Oedema/fluid retention, abdominal pain, dizziness, hypertension, heartburn, epigastric discomfort, diarrhoea, nausea, dyspepsia, headache, pruritus.

Uncommon (>1/1000, <1/100)

Asthenia/fatigue, abdominal distension, chest pain, constipation, oral ulcer, vomiting, digestive gas symptoms, acid reflux, tinnitus, weight gain, muscular cramp, insomnia, somnolence, vertigo, depression, mental acuity decreased, dyspnoea, rash, atopic dermatitis.

In addition, mild hypersensitivity reactions have been reported rarely. The undesirable effect profile was similar in patients treated with rofecoxib for one year or longer

Laboratory adverse experiences

Common (>1/100, <1/10): alanine aminotransferase increased, haematocrit decreased, aspartate aminotransferase increased.

Uncommon (>1/1000, <1/100): BUN increased, haemoglobin decreased, serum creatinine increased, alkaline phosphatase increased, proteinuria, erythrocytes decreased, leukocytes decreased.

Serious side effects associated with the use of NSAIDs

The following serious undesirable effects cannot be ruled out for rofecoxib: nephrotoxicity including interstitial nephritis, nephrotic syndrome and renal failure; hepatotoxicity including hepatic failure and hepatitis; gastro-intestinal toxicity including perforation, ulceration and bleeding; volume overload related toxicity including cardiac failure and left ventricular failure; cutaneo-mucosal adverse effects, severe skin reactions including anaphylactic/anaphylactoid reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

Tablets 12.5 mg and 25 mg: packs of 28 tablets: £21.58.

Oral Suspension 12.5 mg/5 ml and 25 mg/5 ml: bottles of 150 ml: £23.12.

Marketing Authorisation numbers

Tablet 12.5 mg	PL 0025/0383
Tablet 25 mg	PL 0025/0384
Oral Suspension 12.5 mg/5 ml	PL 0025/0385
Oral Suspension 25 mg/5 ml	PL 0025/0386

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK

POM **Date of review:** December 1999

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.
© Merck Sharp & Dohme Limited 1999. All rights reserved.

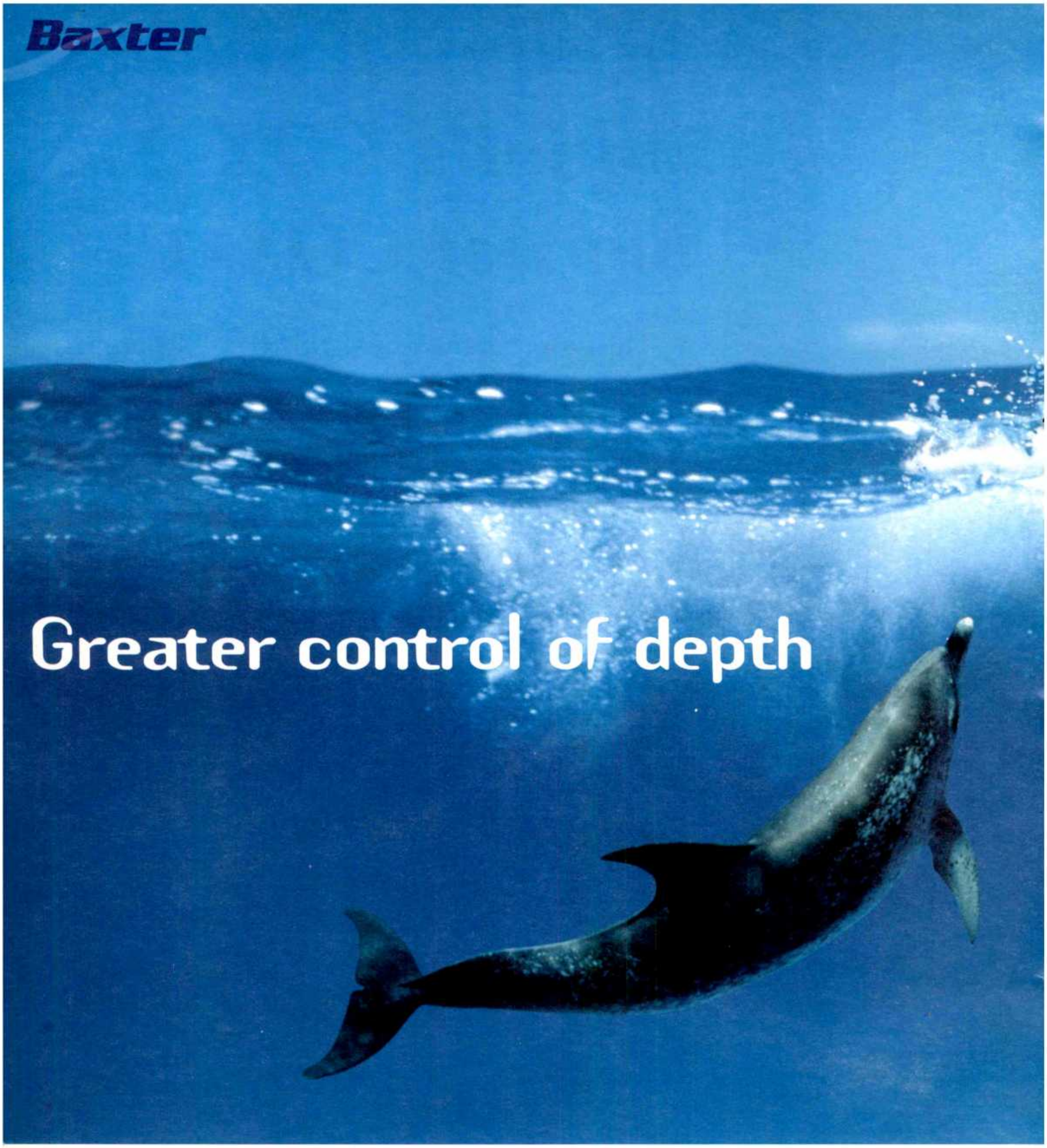
References:

1. Ehrich EW, Dallob A, De Lepeleire I et al. Characterization of rofecoxib as a cyclo-oxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. *Clin Pharmacol Ther* 1999; 65(3):336-347.
2. Data on file, Merck Sharp & Dohme Limited.
3. Laine L, Harper S, Simon T et al. A randomised trial comparing the effect of rofecoxib, a cyclo-oxygenase-2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology* 1999;117:776-783.

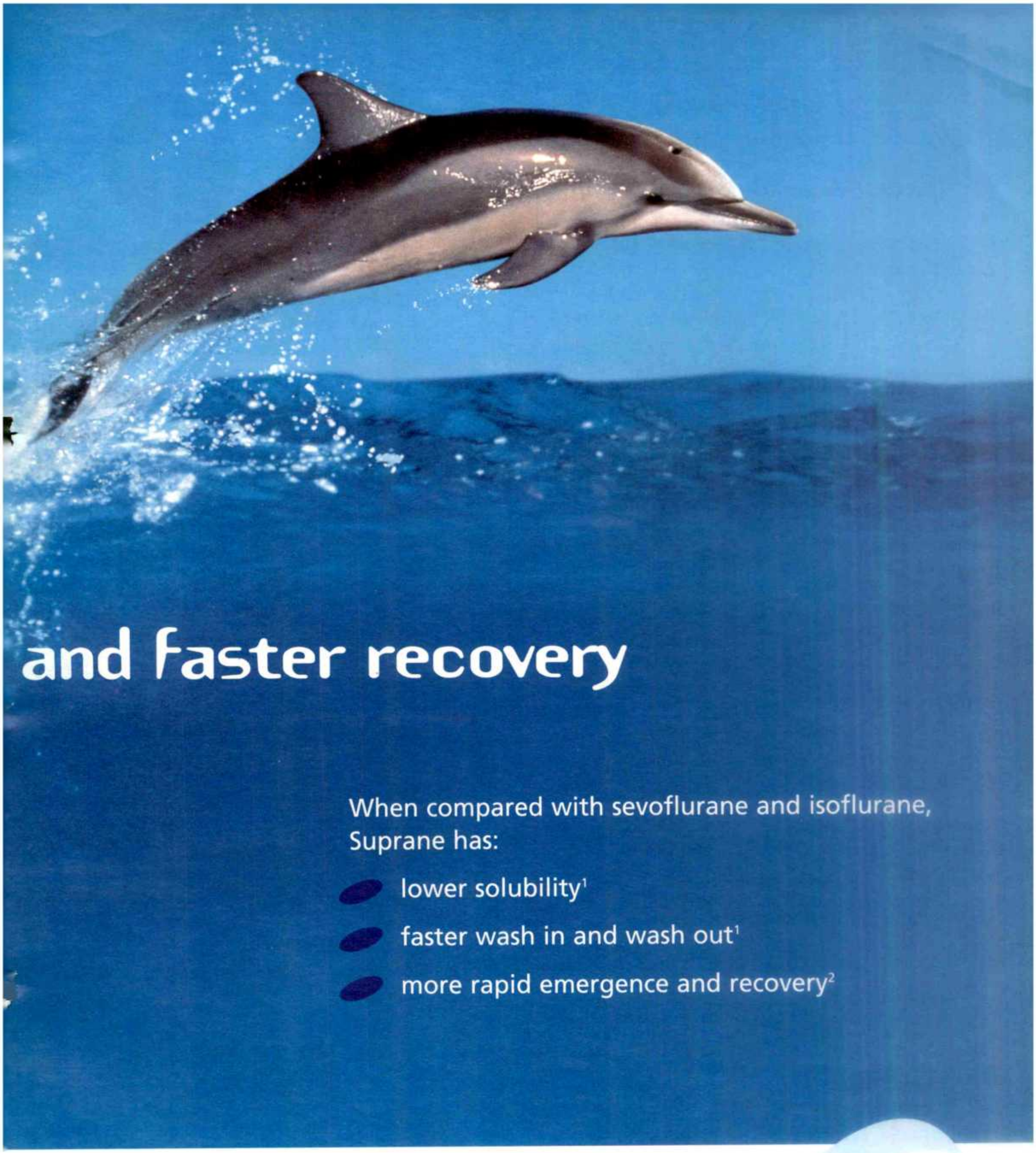
MSD

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

05-00 VOX.99.GB.65619.Jf



SUPRANE® (desflurane) PRESCRIBING INFORMATION
Presentation: Amber glass bottle containing 240ml desflurane, supplied as pure drug substance. Suprane is a volatile liquid for administration by inhalation. Store in an upright position at room temperature (25°C). **Indication:** Inhalation agent for induction and/or, maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery. **Dosage:** Suprane should be administered by trained anaesthetists using a specific vaporiser designed for Suprane. MAC is age-specific and decreases with increasing age. *Induction.* Inspired concentrations of 4-11% of Suprane usually produce surgical anaesthesia in 2-4 minutes. Suprane is not recommended for paediatric induction. *Maintenance.* Surgical anaesthesia may be sustained with 2-6% Suprane when nitrous oxide is used concomitantly. Suprane at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. Concentrations of up to 18% Suprane have been administered for short periods of time, but if high concentrations are used with nitrous oxide, ensure that the inspired mixture contains a minimum of 25% oxygen. Concentrations of 1-4% in nitrous oxide/oxygen have been used successfully in patients with chronic renal/hepatic impairment. **Contraindications:** Suprane should not be used in patients in whom general anaesthesia is contraindicated, in patients with known hypersensitivity to halogenated agents, or in patients with known or genetic susceptibility to malignant hyperthermia. Suprane should not be used for induction in patients at risk of coronary artery disease or where increases in heart rate or blood pressure are undesirable. **Precautions:** Suprane is not recommended for paediatric induction, or for use in neurosurgical patients. Suprane may increase CSF or intracranial pressure in patients with space occupying lesions. A lower concentration is recommended for hypovolaemic, hypotensive and debilitated patients. Sensitivity hepatitis may be caused in patients previously sensitised by exposure to other halogenated anaesthetics. Suprane has been shown to trigger malignant hyperthermia. To minimise the risk of formation of carbon monoxide in rebreathing circuits, carbon dioxide absorbents should not be allowed to dry out. Suprane is not indicated during pregnancy or breast


and faster recovery
When compared with sevoflurane and isoflurane, Suprane has:
lower solubility[1]
faster wash in and wash out[1]
more rapid emergence and recovery[2]

feeding. **Side effects:** Suprane may cause dose-dependent cardio-respiratory depression. Nausea and vomiting have been observed. Hepatitis may occur in patients sensitised by prior exposure to halogenated anaesthetics. In adult induction, cough, breath holding, laryngospasm, apnoea and salivation have been reported. Transient elevations in white blood cell count have been observed. Rare cases of malignant hyperthermia have been reported. No information exists on the effects of Suprane on the ability to drive or operate machinery. An adequate period, at least 24 hours, is needed to ensure full recovery. **Interactions:** Suprane potentiates commonly used muscle relaxants. Lower doses of Suprane are required in those receiving opioids, benzodiazepines, other sedatives, and nitrous oxide. **Overdose:** There is no experience of overdose in humans. Please consult Summary of Product Characteristics for recommendations in the case of overdosing. **Legal category:** POM. **Packs:** Suprane 240ml in amber glass bottles. **Basic NHS price:** £44.41 per bottle. **PL number:** 0116/0327. **PL holder:** Baxter Healthcare Ltd., Caxton Way, Thetford, Norfolk IP24 3SE. **Date of preparation:** December 1999.

® Denotes registered trademark.

References: 1. Eger E I. Anesth. Review. 1993;**20**:87-92. 2. Dupont I et al. Br J Anaesth. 1999;**82**:355-359.

Baxter Healthcare Ltd., Wallingford Road, Compton, Nr. Newbury, Berkshire. RG20 7QW. Tel: 01635 206000

Suprane®
desflurane

Precise control in maintenance anaesthesia

SUP021/UK/0200

McMaster University
Hamilton, Canada

Cardiac Anaesthesia Fellowship

Applications are invited for a Cardiac Anaesthesia Fellowship at Hamilton Health Sciences Corporation, a tertiary regional cardiac centre serving an area from the Niagara Pennisula to the Bruce Peninsula as well as Northwestern Ontario. Annual cardiac surgical volume is over 1,300, providing a full range of cardiac surgical procedures.

Further information is available on the website:

http://www-fhs.mcmaster.ca/anaesthesia/education
or from Mrs Mary Gahagan, Office of the Chair,
Department of Anesthesia, McMaster University,
HSC-2U1, 1200 Main St W, Hamilton,
Ontario, Canada L8N 3Z5
Tel: 01-905-521-2100 ext. 75166
Fax: 01-905-523-1224
E-mail: gahaganm@fhs.mcmaster.ca

ISMETT*

HEART/LUNG TRANSPLANT ANESTHESIA AT UPMC PALERMO
**(l'Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione)*

The University of Pittsburgh Department of Anesthesiology/CCM seeks attending anesthesiologists with fellowship training (or equivalent), for clinical O.R. care of heart/lung transplant recipients in Palermo, Italy. Exciting joint venture of UPMC Health System and the Italian Government. Position involves full time faculty appointment (all ranks) at the University of Pittsburgh, as well as an extremely attractive salary, benefits, and relocation allowance.

Send curriculum vitae and references to:

Leonard Firestone, M.D.
Safar Professor and Chairman
Department of Anesthesiology/CCM
University of Pittsburgh
A-1305 Scaife Hall
Pittsburgh, PA 15261
Fax: (412) 648-1887
E-mail: firestone@anes.upmc.edu

SOCIETY FOR AIRWAY MANAGEMENT

ANNUAL SOCIETY MEETING
WITH HANDS-ON WORKSHOPS

JUNE 2 – 4, 2000

LOEWS LE CONCORDE
Quebec City, Canada

Ulrich Braun, M.D., President
Program Chairman, D. John Doyle, M.D., Ph.D.

The Society For Airway Management (SAM) has been formed with the charter of improving airway management in adults and pediatrics, through research and education. Anesthesiologists, critical care specialists, emergency medicine physicians, otolaryngologists and CRNA's should attend. All aspects of the difficult airway will be covered including special cases pertinent to otolaryngologists and emergency medicine physicians. Hands-on workshops, taught by members of the distinguished faculty, will include training in the following: Adult & Pediatric Fiberoptic Intubation, Lung Isolation, Rigid Fiberoptic Laryngoscopy, Direct Laryngoscopy, Tracheal Light Wand, COPA, LMA, Airway Nerve Block, Combitube and VETT, Cricothyrotomy and Jet Ventilation, Retrograde Intubation, Rigid Bronchoscopy, Rigid Laryngoscopy and Airway Tube Exchangers. For more information or brochure contact:

MMC/UCI Center for Health Education
2801 Atlantic Avenue
Long Beach, CA 90806
(562) 933-0100 or
(562) 933-0101 FAX / britchie@memorialcare.org

OXFORD JOURNALS ADVERTISING

To advertise in
this publication contact
Peter Carpenter

PRC
ASSOCIATES

Advertisement Managers

THE ANNEXE
FITZNELLS MANOR
CHESSINGTON ROAD
EWELL VILLAGE
SURREY KT17 1TF, UK

TELEPHONE: +44 (0)20 8786 7376
FAX: +44 (0)20 8786 7262
EMAIL: mail@prcassoc.co.uk

Editorial Notices

Final FRCA Course

Leicester, May 2–5, 2000

The course will take place at Glenfield Hospital, Leicester and includes lectures, tutorials, mock vivas, mock examinations and video-recorded vivas.

Places are limited so please apply early.

Course fees: £220.00

For further information please contact:

Mrs C. Gethins, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, UK.

Tel: +44 116 258 5291; Fax: +44 116 285 4487; E-mail: chg2@le.ac.uk. Details also on departmental web page: www.le.ac.uk/anaesthesia

The International Forum for all Trauma Team Members

Mainz, Germany, May 4–6, 2000

Hosted by, Clinic of Anesthesiology, Johannes Gutenberg, University of Mainz.

For Anesthesiologists, Emergency Physicians, Intensivists, Surgeons, Pediatricians, Fire Fighters, Paramedics, Anesthesia and Critical Care Nurses.

For further information contact the Organizing Committee:

Markus D. W. Lipp MD, DDS, PhD, Clinic of Anesthesiology, University of Mainz, Langenbeckstr. 1, D-55131 Mainz, Germany.

Fax +49 6131 17 5503; E-mail: golecki@mail.uni-mainz.de

German Congress of Anaesthesiology 2000

Munich May 6–9, 2000

For further information, please contact:

Nadja Schwarz, Project Managment, Medizinische Congressorganisation Nürnberg GmbH, Wielandstraße 6, D-90419 Nürnberg, Germany.
Tel: +49 911 39 3160; Fax: +49 911 33 1204; E-mail: mcn@mcn.nuernberg.de
www:http//www.mcn-nuernberg.de

5th Congress of the European Resuscitation Council 'Resuscitation 2000'

Antwerp, June 1–3, 2000

Congress Director: Prof. Dr Leo Bossaert

For further information, registration and abstracts, please contact:

ERC secretariat, PO Box 113, 2610 Antwerp, Belgium.

Tel: +32 3 821 36 16; Fax: +32 3 828 48 82; E-mail: erc@uia.ua.ac.be; Website: http://www.erc.edu.

For hotel reservation and tours, contact:

Medicongress, Waalpoel 28/34, 9960 Assenede, Belgium.

Tel: +32 9 344 39 59; Fax: +32 9 344 40 10; E-mail: ERC2000@medicongress.com; Website: http://www.medicongress.com/erc.

*Pre-congress courses in BLS, AED, ALS, PLS on May, 29–31, 2000.

M.E.R.I.T. Centre Bradford Royal Infirmary, Bradford, UK – One day course in Spinal Endoscopy

Bradford, UK, June 9, 2000, September 15, 2000 and October 27, 2000

One day course with lectures, practical equipment demonstrations and observation of the technique in patients. Course material includes a comprehensive, practical guide to all aspects of the technique. Instrumentation is state-of-the-art, and it is anticipated that upon completion delegates will be in a position to consider setting up such a service in their own locality. On-going training will be offered.

Of interest to all those involved in the management and investigation of patients with back pain and sciatica as well as those involved with central neural blocks. Numbers of delegates strictly limited. Lunch will be provided.

For further information please contact:

Dr Jonathan Richardson, MERIT Centre, Bradford Royal Infirmary, Bradford, BD9 6RJ.

Tel: +44 1274 364271/364253; Fax: +44 1274 366811; E-mail: merit.centre@mail.bradh-tr/northy.nhs.uk

Frontiers in Anesthesia

Allergy, Immunology, and Anesthetic Action
Ontario, June 10–12, 2000

The conference will take place at Queen's Landing Hotel, Niagara-on-the-Lake, Ontario, Canada.

For further information and registration, please contact:

Centre for Continuing Education, Tulane University Medical Center, 1430 Tulane Ave, TB 51, New Orleans, LA 70112, USA.

Tel: +1 800 588 5300 or +1 504 588 5466; Fax: +1 504 584 1779; E-mail: cme@mailhost.tcs.tulane.edu.

For further details and electronic registration, visit the web page: http://www.tmc.tulane.edu/anes/niagara/

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

World Paediatric Anaesthesia Meeting

Nova Scotia, June 14–16, 2000

The meeting will take place at the Westin Nova Scotian Hotel, Halifax, Nova Scotia, Canada.

For further information, please contact:

Dr. John G. Muir, Division of Paediatric Anaesthesia, IWK Grace Health Centre, 5850 University Avenue, Halifax, Nova Scotia, Canada B3J 3G9.

Fax: +902 428 2911. E-mail: wpam2000@is.dal.ca Visit our web site: www.dal.ca/wpam2000.

Edinburgh Anaesthesia Festival

Edinburgh, August, 23–25, 2000

Organized by the Department of Anaesthetics, Royal Infirmary of Edinburgh, to coincide with the 2000 Edinburgh International Festival of the Arts. The 3-day programme consists of lectures and discussion on current topics in anaesthesia. The lecturers are from all parts of the United Kingdom and represent leading opinions in their field.

For further information: Edinburgh Anaesthesia Festival, University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Tel: +44 131 536 3652; Fax: +44 131 536 3672; E-mail: anaes@ed.ac.uk

The Fifth Annual Symposium of the Association for Low Flow Anaesthesia

Ulm/Neu-Ulm/Germany, September 8–9, 2000

For further information, please contact:

Priv. Doz. Dr Uwe Schirmer, Priv. Doz. Dr Thomas Marx, Department of Cardiac Anaesthesia, University of Ulm, Steinhövelstr. 9, D-89075 Ulm, Germany.

Tel: +49 731 5021521; Fax: +49 731 5026757; e-mail: alfa2000@gmx.net; congress homepage http://www.uni-ulm.de/alfa2000.

XIX Annual Congress of the European Society of Regional Anaesthesia Joint Annual Congress with EuroPain 8th European Conference on Pain Research

Rome, Italy, September 20–23, 2000

The congress will be held in the Sheraton Hotel.

Abstract deadline is June 1, 2000.

For further information, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 5643; Fax: +032 2 346 5435;
E-mail: dionne@options.com.cy

Surfactant 2000

From Trier to Basle September 23–29, 2000

This is an international floating congress on the rivers Mosel and Rhine. All aspects of surfactant (basic science/clinical applications) will be addressed.

For further information, please contact:

Dr B. Lachmann, Department of Anesthesiology, Erasmus University Rotterdam, Postbox 1738, 3000 DR Rotterdam, The Netherlands.
Web site: http://www.floating-congress.vet.uu.nl

Dingle 2000 – Current Controversies in Anaesthesia and Perioperative Medicine

Dingle, County Kerry, Ireland, October 4–8, 2000

University College London Hospitals Centre for Anaesthesia announce a call for abstracts: there is an opportunity to submit work for poster presentation and selected finalists will be invited to give an oral presentation (prizes totalling £1000). Any research is acceptable provided it has not been published in any peer reviewed journal by the abstract deadline of 30 June 2000.

For further abstract and meeting registration details please contact:

Dr Monty Mythen, Centre for Anaesthesia, Room 103, 1st Floor Crosspiece, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK.

Tel: +44 20 7380 9477; Fax: +44 20 7580 6423;
E-mail: uch.acru@btinternet.com

European Academy of Anaesthesiology European Diploma in Anaesthesiology and Intensive Care

Part I (MCQ), October 7, 2000

(Endorsed by the European Board of Anaesthesiology (EBA) of the Union of European Medical Specialists (UEMS)

This examination will be held in English, French, German, Italian and Spanish in Athens, Barcelona, Berne, Budapest, Cluj-Napoca, Göttingen, Liège, Ljubjlana, London, Lund, Moscow, Oslo, Paris, Poznan, Riga, Rome, Tel Aviv, Uppsala and Vienna.
Regulations and application forms are available from:

Examinations Manager, European Academy of Anaesthesiology, London House, 243 Lower Mortlake Road, Richmond, Surrey TW9 2LS, UK.
Tel: +44 (0)208 940 6240; Fax: +44 (0)208 940 6262; E-mail: DEAA@compuserve.com; Home page: http://eaa-web.eu.org

The closing date for receipt of applications is May 31, 2000 (fee: £170)
Applications received after the closing date or unaccompanied by the full fee cannot be accepted and will be returned.

Wood Library-Museum's Quadrennial Laureate of the History of Anesthesia Prize

Members of the Editorial team of the *BJA* are pleased to announce that, Dr Thomas B. Boulton (UK) and Dr Norman

A. Bergman (USA) are to be awarded the Wood Library – Museum's quadrennial Laureate of the History of Anesthesia Prize at the annual meeting of the American Society of Anesthesiologists in October 2000, in San Francisco.

We offer our hearty congratulations to Dr Boulton, and to the family of Dr Bergman, who unfortunately died recently.

St Bartholomew's Hospital Choral Society

Royal Albert Hall, London, UK, November 21, 2000

St Bartholomew's Hospital Choral Society celebrates the millennium and their 35th anniversary with the Royal Medical Benevolent Fund as their chosen Charity for their season 2000/2001.

Mahler's Symphony No. 8 'Symphony of a Thousand' with the Royal Philharmonic Orchestra, Royal Albert Hall, 21 November 2000.

It needs a *really* big choir, splendid orchestra, fine soloists and conductor. Six hundred singers are needed for this monumental work.

To participate contact the Barts Choir Honorary Secretary on:

Tel: +44 1628 664157.

Or to support, details available from:

The Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN.

Tel: +44 20 8540 9194; Fax: +44 20 8542 0494;
E-mail: rm.bf@virgin.net

11th Congress, Western Pacific Association of Critical Care Medicine

Singapore November 29–December 3, 2000

This meeting will take place at the Westin Stamford and Westin Plaza, Singapore and is organized by the Society of Intensive Care Medicine (Singapore).

For further information, please contact:

11th WPACCM Congress Secretariat, Academy of Medicine, Singapore College of Medicine, Building 16, College Road, #01-01, Singapore 169854.
Fax: +65 225 5155; E-mail: monicaw@pacific.net.sg

19th Annual Symposium Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

San Juan, Puerto Rico, January 13–20, 2001

Free Papers will be accepted for oral and poster presentation in four categories: (i) monitoring; (ii) new pharmacological agents; (iii) interesting case reports; (iv) cardiopulmonary bypass technology. Abstracts forms are available upon request. The deadline for submission is November 1, 2000. Tuition will not be waived. Brochure available in June 2000.

For information and abstract forms contact: Helen Phillips, Box 1010, Mt. Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029-6574, USA.

Tel: +1 212 241 7630; Fax: +1 212 426 2009; E-mail: helen_phillips@smtplink.mssm.edu

2nd International Conference on Pain Control and Regional Anaesthesia

Jaipur, India, February, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA 4th Workshop 'Neural Blockades on Cadavers'

(European Society of Regional Anaesthesia)

Innsbruk, Austria, February 22–24, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESA 8th Annual Congress

(European Society of Anaesthesiologists)
Gothenburg, Sweden, April 10, 2001

Abstracts deadline: December 1, 2000

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

16th Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists (EACTA)

Weimar, Germany, May 16–19, 2001

For further information please contact:

Anita Akabogy, Congress Department, MCN Medizinische Congress-organisation Nürnberg AG, Zerzabelshofstrasse 29, 90478 Nuernberg, Germany.

Tel: +49 911 393 16 10; Fax: +49 911 393 16 55; E-mail: akabogu@mcn-nuernberg.de; www: http://www. mcn-nuernberg.de

German Congress of Anaesthesiology 2001 (DAK 2001)

Messezentrum Nürnberg, June 13–16, 2001

International Symposium on Anaesthesiological and Surgical Perspectives of Ambulatory Surgery in the New Millennium

Stockholm, Sweden, August 30 - September 1, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

ESRA XX Annual Congress

(European Society of Regional Anaesthesia)
Joint Annual Congress with EuroPain 9 European Conference on Pain Research

Warsaw, Poland, September 19–22, 2001

Abstracts deadline: May 15, 2001

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

8th World Congress of Intensive and Critical Care Medicine

Sydney, Australia, October 28–November 1, 2001

For further information please contact:

Congress Secretariat, 8th World Congress of Intensive and Critical Care Medicine, GPO Box 2609, Sydney, NSW 2001, Australia.

Tel: +61 2 9241 1478; Fax: +61 2 9251 3552; e-mail: iccm@iccmsaust.com.au; website: www.iccm.aust.com

First World Congress on Regional Anaesthesia and Pain Therapy

Barcelona, Spain, June 5–8, 2002

For further information on the congress, please contact:

Options Eurocongress, Ms Dionne Bosma, Rue Washington 129, B-1050 Brussels, Belgium.

Tel: +32 2 346 53 01; Fax: +32 2 346 36 37; E-mail: dionne@options.com.cy

German Congress of Anaesthesiology 2002 (DAK 2002)

Messezentrum Nürnberg, June 26–29, 2002

German Congress of Anaesthesiology 2003 (DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Awareness during Anesthesia—The 2000 *Anesthesiology* Journal-sponsored Symposium at the ASA Meeting

San Francisco, California, October 17, 2000, 9:00–12:30

The moderators will be Alex S. Evers MD (Washington University, St Louis) and Richard B. Weiskopf MD (University of California, San Francisco)

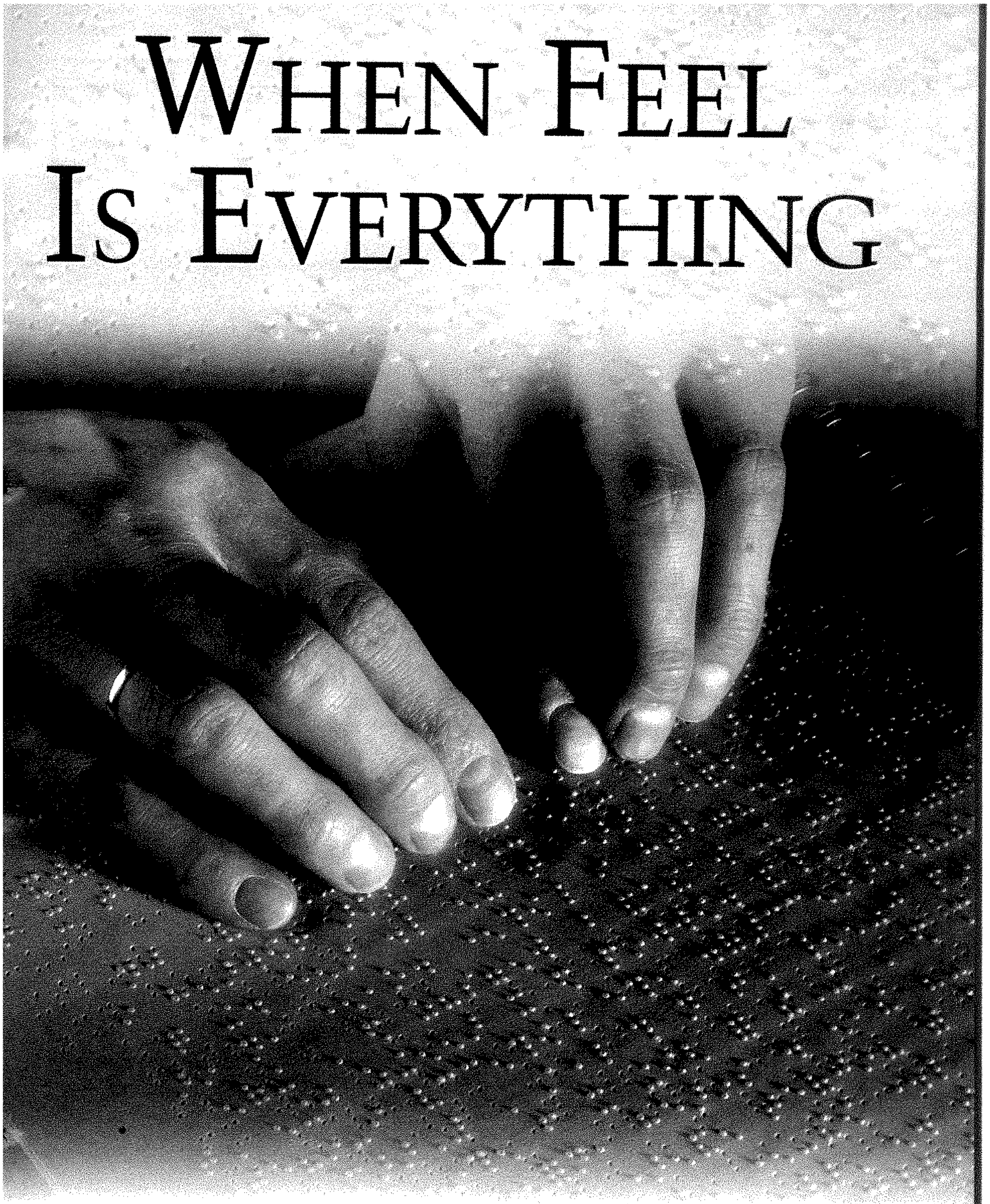
Awareness during anaesthesia is a potential problem of concern to clinicians and the public. There are clear cases of patients having been unintentionally awake during anesthesia and surgery and other cases for which 'awareness' was not as clearly delineated. 'Awareness' during anaesthesia and surgery can result in 'post-traumatic stress syndrome'.

This symposium will include invited speakers and a discussion session, as well as an opportunity to view selected abstracts. Abstracts in the following areas are considered appropriate for submission:

(i) epidemiology of 'awareness' during anaesthesia,
(ii) monitoring of depth of anaesthesia,
(iii) prevention of awareness during anaesthesia,
(iv) treatment of syndromes resulting from awareness during anaesthesia.

Abstracts should be submitted via the regular Annual Meeting procedures by April 1, 2000. *Online submission is available.* Abstracts requesting consideration for presentation at this symposium will undergo an additional review in addition to the standard ASA abstract review process. If you would specifically like your abstract considered for inclusion in the symposium, please check the special box that can be found on the cover letter/form which must accompany your submission. If you need abstract submission materials, please contact the American Society of Anesthesiologists:

American Society of Anesthesiologists, 520 N. Northwest Highway, Park Ridge, IL 60068–2573, USA.
Tel: +1 847 825 5586; Fax: +1 847 825 1692;
E-mail: mail@ASAhq.org Web site: http://www.asahq.org



WHEN FEEL IS EVERYTHING

SIMS is a world leading medical manufacturing group, with companies in Europe, North America, South Africa and the Pacific region, providing innovative products to critical care and community care professionals worldwide.

CSEcure

Combined Spinal Epidural Needle System

CSEcure's unique design provides confidence and control without compromising tactile feel.
So when you perform a procedure where feel is everything, feel CSEcure.
Visit our website today: www.portex.com

SIMS Portex

SIMS
SMITHS INDUSTRIES
Medical Systems
INNOVATION IN CRITICAL AND COMMUNITY CARE

For further information, please call SIMS Portex on +44 (0) 1303 260551. SIMS Portex Limited, Hythe, Kent, CT21 6JL, UK. E-Mail: export.sales@portex.com or uk.sales@portex.com
'CSEcure', 'SIMS', and 'SIMS Portex' - SIMS Trademarks

Meeting Announcement

TEMPERATURE AND ACUTE CARE

Chaired by: Dr Mahesh Shah

Thursday, 29 June 2000

Rupert Beckett LectureTheatre, University of Leeds

Thermoregulation and Anaesthesia

Dr Charles Deakin, Southampton

Effects of Temperature Changes on Organ Systems

Dr Angus Crossley, Derby

Temperature Regulation in the Critically ill Patient

Dr Andrew T Cohen, Leeds

Techniques to Regulate and Measure Temperature

Dr Bryn Baxendale, Nottingham

Temperature Care in the Accident and Emergency Dept

Mr Paul Grout, Hull

TEMPERATURE AND WOUND CARE

Chaired by: Professor Leaper, North Tees

Does Warming Therapy Prevent Pressure Ulcers?

Ms Eileen Scott, North Tees

Post Surgical Wound Infections in Day Case Surgery

Mr Andy Melling, North Tees

CME approval and RCN accreditation has been applied for

Registration Fee: £60.00 medical; £30.00 nursing
Cheques made payable to "Leeds Anaesthetic Meeting"
SUPPORTED BY AN EDUCATIONAL GRANT FROM ACTAMED

Please contact : Jennie Smith, Dept of Anaesthesia,
Leeds General Infirmary, Great George Street, Leeds LS1 3EX.
Tel: 0113 392 6672. Email:smithje@ulth.northy.nhs.uk

NIH-FUNDED RESEARCH FELLOWSHIP

(2 years)

COLUMBIA UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

Candidates must have completed at least 2.5 years of residency, have strong interest in an academic career, and must be citizens or permanent residents of the U.S. Training program individualized according to research interest. Trainees may work with mentors within the Department of Anesthesiology or faculty members in basic science departments on the Health Sciences campus. Many areas of research are currently available. They include molecular mechanisms of anesthetic action, endothelial cell function, fetal response to hypoxia, cocaine toxicity and metabolism, cerebral vascular physiology, developmental cardiac autonomic pharmacology and cardiac electrophysiology.

Interested candidates should call or write:

Dr . Margaret Wood, Professor and Chairman,
Department of Anesthesiology, Columbia University,
College of Physicians and Surgeons,
630 West 168th Street, New York, NY 10032.
Tel: (212) 305 3117, Fax: (212) 305 3296.

Columbia University is an Equal Opportunity / Affirmative Action Employer

Special Rates Available

to companies and organizations

Articles relevant to your company or organisation can be reprinted for circulation at seminars, conferences and exhibitions, so that key individuals are kept fully up to date with the latest opinions, developments and status of your products, technologies and techniques.

Bulk subscriptions including your organizational logo, can be sent to those who practice at the forefront of your field, helping to raise your profile and underline your reputation

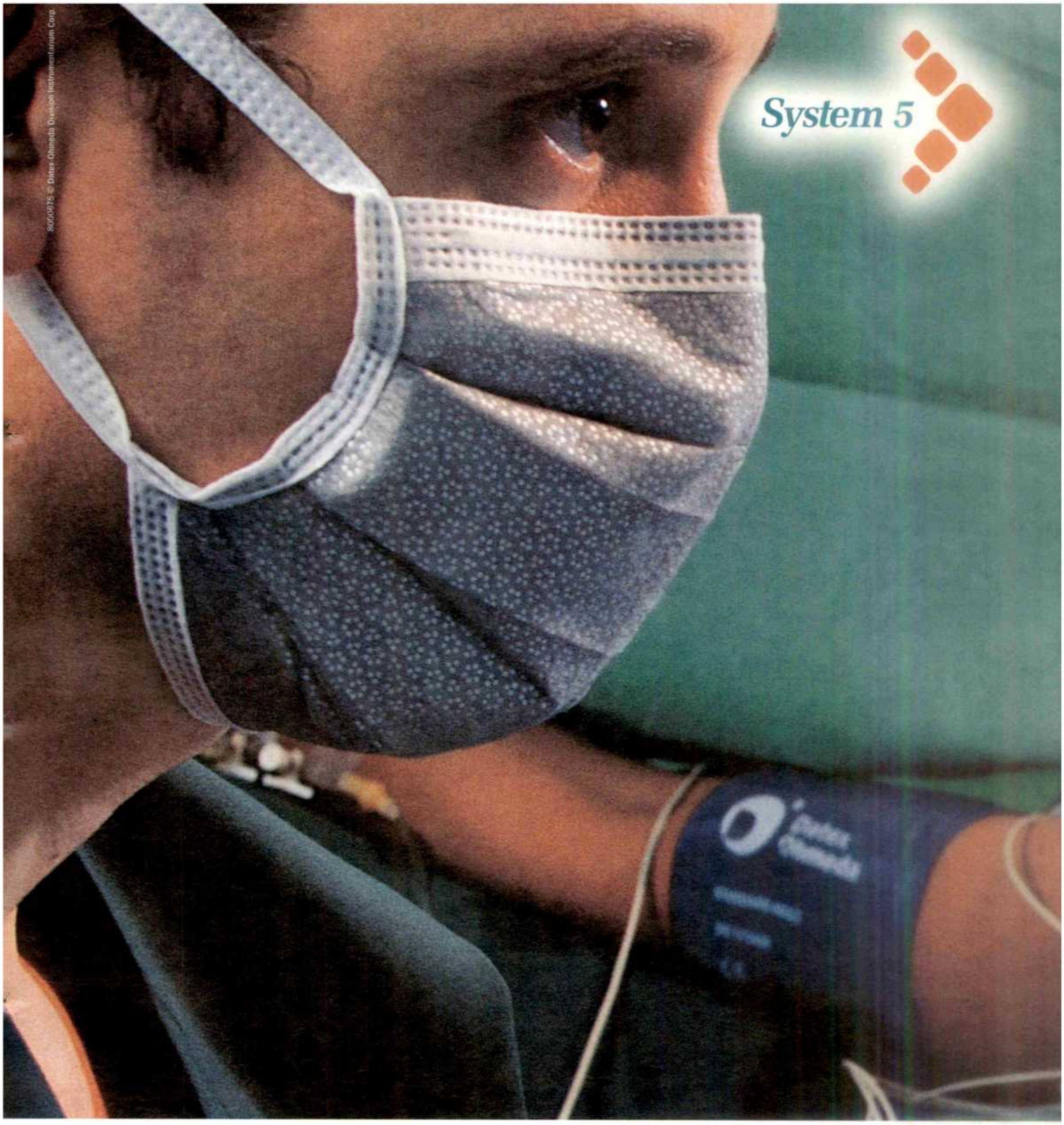
Supplement proposals covering development and research or seminars and conferences are often considered by us, and once published, are always mailed to a highly targeted readership, ensuring that those who really need to know do know.

Contact:
Gerry Lincoln/Julie Gribben
Special Sales Department
Journals Division
Oxford University Press
Great Clarendon Street
Oxford, OX2 6DP, UK
tel: +44 (0) 1865 267827
fax: +44 (0) 1865 267774
or visit **www.oupjournals.org**

Oxford Journals Reprints, Supplements and Corporate Subscription Service

OXFORD

Selling Ideas



Soft landing

They say anesthesia is like flying an airplane.
Taking off and landing are the riskiest phases.
Landing your patient softly in recovery
will never be routine.

Datex·Ohmeda
Devoted to caring for life

JOINT
"ESRA-ESOA CONGRESS 2000"

ESRA
EUROPEAN SOCIETY OF
REGIONAL ANAESTHESIA

ESOA
EUROPEAN SOCIETY OF
OBSTETRIC
ANAESTHESIOLOGY

18-21 MAY 2000
DIVANI APOLLON PALACE HOTEL
KAVOURI, ATHENS GREECE

"60 Renowned Speakers from across the globe"

"20 years Progress and into the Millennium"

JOINT SCIENTIFIC PROGRAMME

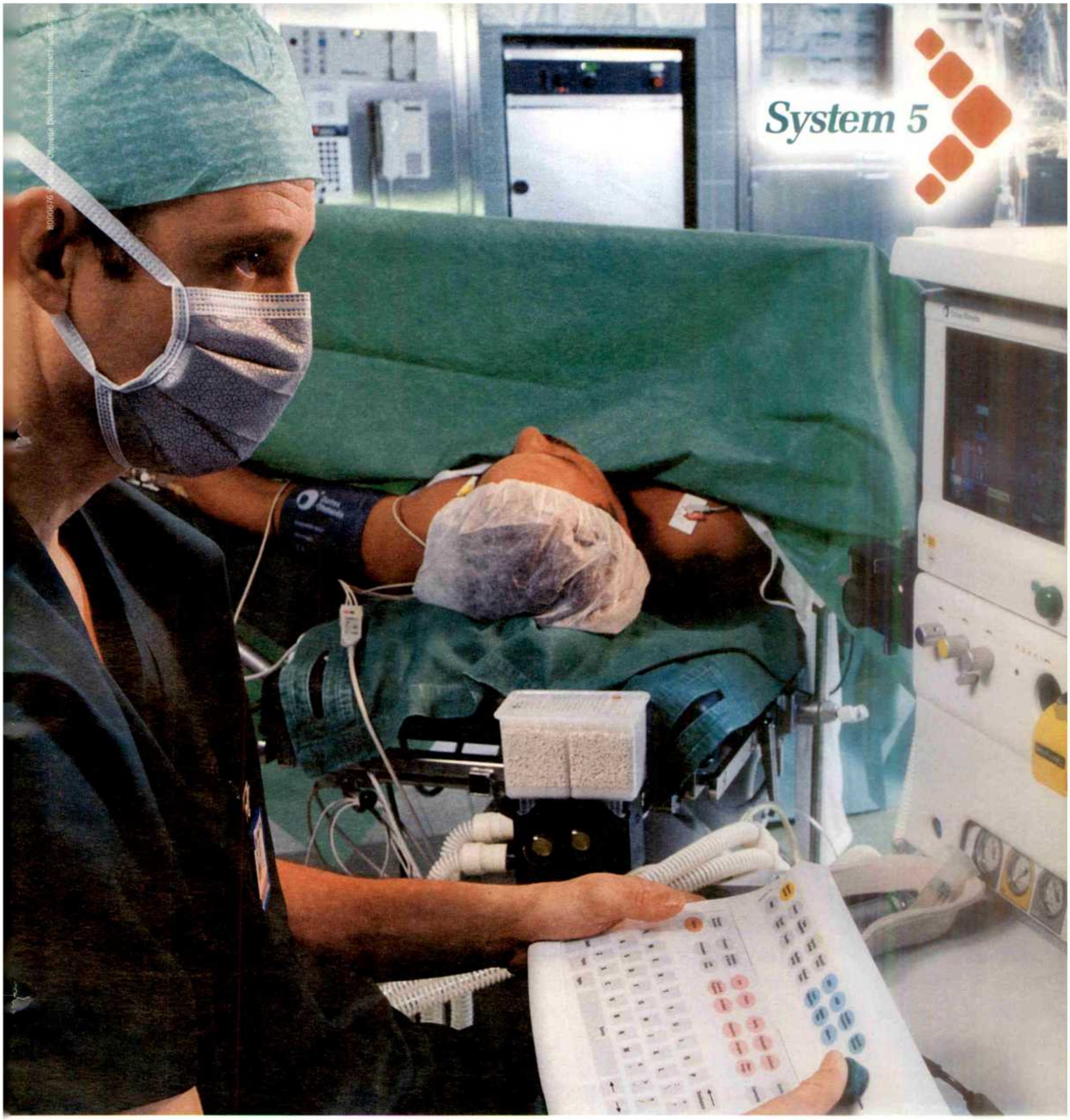
ESRA - 2nd Mediterranean & Balkan Congress of Regional Anaesthesia and Pain Therapy

- The Past, the Present and the Future of Regional Anaesthesia
- History of Regional Anaesthesia
- Risk & Benefits of Regional Anaesthesia
- Acute Pain Management
- Chronic Cancer Pain Relief
- Advances towards the New Millennium in Spinal Needles
- Nursing Care in Acute & Chronic Pain Management & Palliative Care
- New Concepts in Regional Anaesthesia, Obstetrics and Paediatrics
- New Horizons in Neuropathic Pain
- Non-Steroidal Anti-inflammatory Drugs - The role in Post-Operative Pain
- Regional Anaesthesia and Neurological Complications
- New Trends in Pain Research
- Peripheral Nerve Blocks
- Opioids and Non Malignant Pain
- Adjuvants in Regional Anaesthesia
- Present and Future use of Anaesthesia: General and Regional Anaesthesia in the New Millennium?

ESOA - VII Annual European Congress of t European Society of Obstetric Anaesthesiol

- ❖ Does Obstetric Anaesthesia influence Maternal Morbidity and Mortality?
- ❖ What's New in Epidural Analgesia for Obstetrics.
- ❖ Continuous Analgesia with Ropivacaine for Labour and Delivery
- ❖ How to improve Pain Relief during Labour.
- ❖ Anaesthesia for Surgery during Pregnancy.
- ❖ Are there New Agents in Obstetric Anaesthesia?
- ❖ Monitoring in Obstetric Anaesthesia.
- ❖ Pain Control in Obstetric Anaesthesia - Today's Anaesthesia and towards the new Millennium.
- ❖ Complications in Regional Anaesthesia for Obstetrics.
- ❖ Combined Spinal Epidural.
- ❖ Prophylaxis of Pulmonary Aspiration - Advances in Antiemetics.
- ❖ The Role of Opioids in Obstetrics.
- ❖ Perinatal Physiology.
- ❖ High Risk Pregnancy.

Congress Organisers & Secretariat
Options Eurocongress
78 Syngrou Ave., 11742 Athens, Greece,
Tel: +30 1 922 2161 / 0510 Fax: +30 1 922 2298
e-mail: options@oe.ath.forthnet.gr

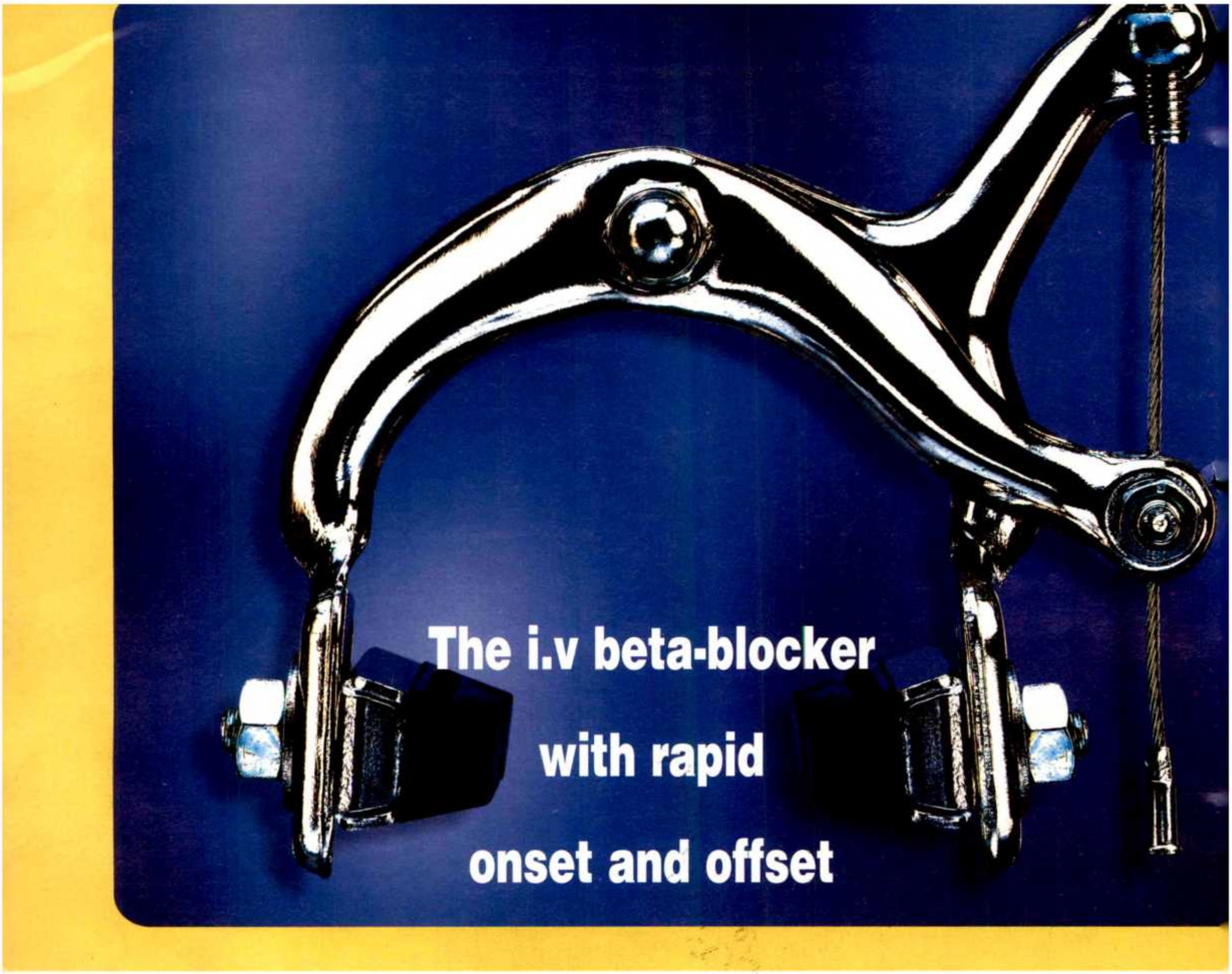


New awakening

System 5 is Datex-Ohmeda's new product family. It holds everything we know about anesthesia and critical care. From pre-operative assessment to recovery.

Contact your nearest Datex-Ohmeda partner. Let's discuss System 5 and new opportunities.

Datex·Ohmeda
Devoted to caring for life



BREVIBLOC is a short acting cardioselective iv beta-blocker.

Because of its 2 minute onset and 9 minute half-life, Brevibloc provides rapid and precise control of heart rate, blood pressure and is indicated for control of SVTs including atrial fibrillation and flutter

Brevibloc

(esmolol HCI)

BREVIBLOC ® (esmolol HCl)
PRESCRIBING INFORMATION

Please refer to the data sheet before prescribing. **Presentation** Ampoules containing 2.5g esmolol hydrochloride in 10ml sterile aqueous concentrated solution (250mg/ml) to be diluted before intravenous administration. Vials containing 100mg esmolol hydrochloride in 10ml sterile aqueous solution (10mg/ml) for intravenous administration without dilution. **Uses** For the short-term treatment of tachycardia and hypertension occurring in the perioperative period and supraventricular tachyarrhythmias including atrial fibrillation, atrial flutter and sinus tachycardia. **Dosage and administration** BREVIBLOC 2.5g CONCENTRATE MUST BE DILUTED BEFORE INFUSION with an appropriate intravenous fluid to give a final concentration of 10mg/ml and infused into a large vein. Brevibloc 100mg is a ready-to-use preparation at a concentration of 10mg/ml. The following dose regimens may be used. a. For intraoperative treatment - during anaesthesia when immediate control is required, give an 80mg loading bolus over 15-30 seconds followed by a 150 micrograms/kg/min infusion. Titrate the infusion rate as required up to 300 micrograms/kg/min. b. Upon awakening from anaesthesia - administer an infusion of 500 micrograms/kg/min for four minutes followed by a 300 micrograms/kg/min infusion. c. For post-operative situations - when time for titration is available give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150, 200, 250 and 300 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. d. For supraventricular tachyarrhythmias - give the 500 micrograms/kg/min loading dose over one minute before each titration step to produce a rapid onset of action. Use titration steps of 50, 100, 150 and 200 micrograms/kg/min given over four minutes, stopping at the desired therapeutic effect. **Contra-indications, warnings, etc.** *Contra-indications* Brevibloc is contraindicated in patients with sinus bradycardia, heart block greater than first degree, cardiogenic shock and overt heart failure. There is no experience with Brevibloc in pregnancy and, although animal tests have shown no teratogenic effect, the use of Brevibloc in women where pregnancy is suspected or confirmed should be avoided. *Warnings and precautions* Use with caution in patients with bronchospastic disease or impaired renal function or diabetes. Brevibloc should also be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities and Brevibloc should not be administered within 48 hours of discontinuing verapamil. The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Brevibloc. The dosage of either agent may be modified as needed to maintain the desired haemodynamics. Infusi concentrations of 20mg/ml have been associated with significant veno irritation and thrombophlebitis in animals and man. Extravasation 20mg/ml may lead to a serious local reaction and possible skin necros Concentrations greater than 10mg/ml or infusion into small veins through a butterfly catheter should be avoided. *Use in Children* T safety and effectiveness of Brevibloc in children have not be established. *Use in Elderly* Analysis of data from 252 patients over years of age indicated no variations in pharmacodynamic effec however no special studies in the elderly have been conducted. **Adver effects** Most frequently observed side effect has been hypotensi Other reported side effects have included bradycardia a bronchospasm. **Pharmaceutical precautions** BREVIBLOC 2. CONCENTRATE MUST BE DILUTED BEFORE USE. BREVIBLOC NOT COMPATIBLE WITH SODIUM BICARBONATE. **Legal catego** Prescription Only Medicine. **Basic NHS. price** Brevibloc 2.5g 10 Concentrate Ampoule £65.90; Brevibloc 100mg/10 ml Vial pack of £29.50. **Productlicenceholder and number** Baxter Healthcare Limite Caxton Way, Thetford, Norfolk, IP24 3SE. Brevibloc 2.5g Concentra PL 0116/0318; PA 167/99/2. Brevibloc 100mg/10ml Vial - PL 0116/031 PA 167/99/1. **Date of Preparation** July 1998 ® Denot registered trademark

Baxter

©2000 Baxter Healthcare Ltd

Baxter Healthcare Ltd
Wallingford Road
Compton, Nr Newbury
Berkshire, RG20 7QW.
Tel: 01635 206000

BVC011/UK/0200

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 84, Number 4, April 2000

Editorial I

Hot air or full steam ahead? An empirical pharmacokinetic model of potent inhalational agents

Potent inhalational agents were the first drugs used in general anaesthesia, approximately 150 yr ago. Before the introduction of the calibrated vaporizer they were introduced into the breathing system by bolus injection, much like our current practice with most intravenous anaesthetic drugs. Dose size (ml of fluid) and interdose intervals were determined by the clinician's experience and the observed patient response. The calibrated vaporizer did away with these imprecise methods. It enabled the anaesthetist to precisely and deliberately alter the concentration of anaesthetic released into the fresh gas flow. With a calibrated vaporizer, the anaesthetist needed only a rough idea about the time constants influencing the equilibration between the inspired gas and the anaesthetic effect, and could directly dial in a partial pressure (concentration) and establish the desired 'depth of anaesthesia'. No fancy mathematics were needed. With the availability of breath-to-breath gas analysers. which have been a mainstay of any modern anaesthesia workstation since the late 1980s, the availability of end-expiratory (alveolar) concentrations did away with the guesswork about most time constants. Alveolar (presumably arterial) partial pressure is one time constant short of the 'real stuff', the concentration in the brain. This time constant, called ke_0, has been determined for isoflurane, sevoflurane (both 0.29 ± 0.04 min^{-1}) and desflurane (0.61 ± 0.11 min^{-1}) using the 95% spectral edge of the EEG power spectrum as an endpoint.[1] The corresponding equilibration half-times amount to 2.4 min for both isoflurane and sevoflurane and 1.1 min for desflurane, implying fast equilibration between arterial and cerebral concentrations. The clinical anaesthetist therefore knows the actual partial pressure at the effect site (concentration) quite well, a situation that can never be achieved for injectable anaesthetics. So why do the pharmacokinetics of volatile anaestheticsvolatile anaesthetics at all?

First, we have to be able to characterize the pharmacokinetic behaviour of new volatile agents. Second, the availability of several agents necessitates comparison of their pharmacokinetic properties in order to rationally select the best agent for a certain surgical procedure. Third, since every individual is unique, we need to identify the characteristics (e.g. weight, age and, gender) that predict individual deviation from 'standard' pharmacokinetics. Physiological flow- and partition-based models are entirely adequate for the characterization of a new agent and the type of simulation required for rational drug selection.[1 2] However, physiological models are relatively complex. Additionally, it is impossible to fit all parameters by observing the time course of alveolar ventilation, and the fraction inspired and fraction exhaled, as available from clinical data. Thus, physiological models are not well suited for the analysis of partial pressure versus time curves obtained in a clinical setting For this task, a parsimonious empirical polyexponential model similar to those used to describe the concentration time course of injectable drugs would be preferable.

In this issue of the *British Journal of Anaesthesia*, Rietbrock and colleagues describe a methodology for developing parsimonious empirical models from routine clinical data.[3] In an accompanying companion manuscript, Wissing and colleagues describe the details of such models for three commonly used inhaled anaesthetics: isoflurane, sevoflurane, and desflurane.[4] Application of these models to vast numbers of patients undergoing general anaesthesia with potent volatile anaesthetics will enable researchers to establish databases containing hundreds of observation units and to perform covariate analyses from routine clinical data, the dream of every population pharmacokineticist. Highly useful models can be developed by combining Wissing's approach with patient covariates (e.g. age, height and weight), and measures of alveolar ventilation, administered concentration, exhaled concentration and the corresponding times.

In Wissing's study of 48 patients, the type of procedure and the patient population were quite homogeneous, resulting in a homogeneous anaesthetic time course Furthermore, at the end of their observations it appears that 76% of the desflurane, 90% of the isoflurane, and 91% of the sevoflurane remained in the body These are conspicuously high values compared with accepted values for conventional pharmacokinetic analysis of intravenously administered drugs. Therefore we suspected that the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

model predictions would only be similar to those of a physiological model at and below a duration of administration of 2 h, and suspected that the model might mispredict concentrations during the wash-out after a longer duration of anaesthesia.

We decided to do a little stress testing on our own. We implemented the pharmacokinetic model with the respective parameter sets by Wissing and colleagues for each agent in NONMEM. Then we simulated the uptake behaviour administering 1 MAC inspired and the wash-out behaviour after inhalation of 1 MAC inspired for 1 h, 2 h, 4 h, and 12 h for each volatile anaesthetic. All simulation results were displayed graphically as wash-in/wash-out curves.

For comparison, we repeated all simulations with GasMan, a commercially available simulation program written by James Philip, MD. GasMan is based on a physiological model of uptake and distribution of volatile anaesthetics.[5] Since this program does not allow data export to a spreadsheet for entire wash-out curves, we could only compare single-point GasMan predictions with the wash-in/wash-out curves mentioned above. Since the wash-in and wash-out behaviours of potent volatile anaesthetics differ considerably, these points were chosen on the basis of reaching a certain concentration predicted by GasMan rather than using fixed times regardless of agent.

For wash-in, we compared the end-expiratory (alveolar) concentrations at 0.3, 0.5 and 0.9 MAC in the alveolar space. For wash-out, we compared end expiratory concentrations at the time of termination of administration (1 h, 2 h, 4 h, and 12 h), at 0.5 and 0.33 MAC alveolar concentrations and 0.5, 0.33, 0.2 MAC concentrations in the so-called vessel-rich group (VRG). This was done to get comparisons at clinically relevant concentration time points. The VRG resembles the effect site most closely in the physiological model implemented in GasMan. A MAC value of 0.2 in the VRG is somewhat lower than MAC awake and should correspond to extubation in almost all patients. Comparisons at lower concentrations were deliberately omitted since they have little clinical relevance. The wash-in predictions are displayed in Figure 1, graph A. Graphs B, C, D, and E show the wash-out behaviour after administration of anaesthetic vapour for 1, 2, 4, and 12 h, respectively.

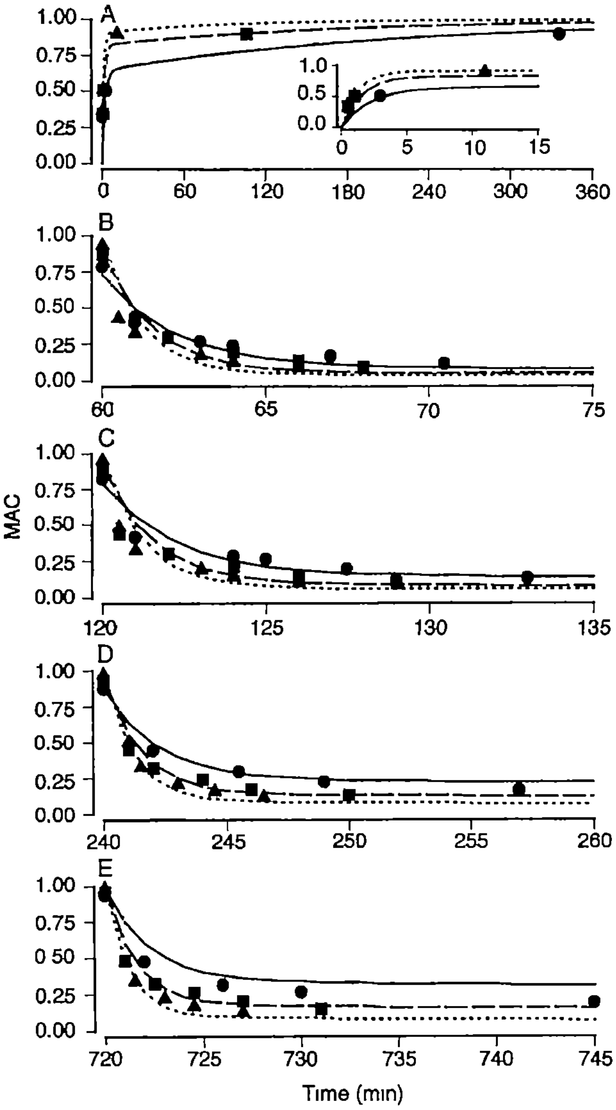


Fig 1 Wash-in and wash-out of isoflurane, sevoflurane and desflurane as predicted by a physiological model (GasMan) and by the empirical polyexponential model reported by Wissing and colleagues The symbols refer to predictions made by GasMan (● isoflurane, ■ sevoflurane, ▲ desflurane); the curves are derived from pharmacokinetic simulations based on the parameter sets reported by Wissing (– isoflurane, – – sevoflurane, — desflurane). (A) Wash-in more than 6 h. (B) Wash-out after breathing 1 MAC for 1 h. (C) Wash-out after breathing 1 MAC for 2 h. (D) Wash-out after breathing 1 MAC for 4 h (E) Wash-out after breathing 1 MAC for 12 h.

Before to accepting GasMan as the gold standard for this comparison, we had to test the predictions of GasMan against the empirical model under conditions resembling those of the study. Models should predict correctly at or below actual sampling times under conditions used for their development. Discrepancies here would have invalidated the entire approach. In our opinion, as can be seen in Figure 1, graphs A, B, and C, there is sufficient agreement between GasMan and the parsimonious model to accept the testing conditions. With the exception of the earliest assessment (fractional expired of 0.33 MAC), the predictions of wash-in behaviour match the models well. The poor early prediction is probably the result of the inability of Wissing's model to distinguish between the alveolar, arterial and vessel-rich compartments, which are lumped together into a virtual central compartment and, because of the absolute magnitude of error (1–2 min), are not critical. A similar error can also be seen in the early part of the 1 h and 2 h wash-out curves, and the explanation is probably the same.

We then examined the behaviour of the model for different anaesthetic conditions other than those in the original study. When comparing predictions after longer administration times, the correlation works surprisingly well for sevoflurane and desflurane, but breaks down for isoflurane. Wissing's model predicts that patients would have a hard time to ever awaken from isoflurane anaesthesia of ≥4 h. How can we explain this peculiarity? Fundamentally, pharmacokinetics should not be extrapolated beyond the domain of the original research. This is particularly true for drugs with significant accumulation in fat, where short studies may mistake uptake into fat for systemic elimination, thereby underestimating the terminal elimination half-life. If one wants to predict pharmacokinetics for <4 h of anaesthetic administration, then the pharmacokinetics should be based upon ≥4 h of data.

In summary, the manuscript of Wissing and colleagues introduces a pharmacokinetic model of volatile anaesthetics that may be highly useful for covariate analysis and population pharmacokinetics. We are looking forward to seeing this model used in follow-up studies to refine the parameter sets with anaesthetics of longer duration. Additionally, we are looking forward to seeing these models used in population analyses to characterize mean pharmacokinetics, important patient covariates, and population-based simulations.

T. Bouillon[1]
S. L. Shafer[2]
[1]*Resident, Department of Anesthesiology and Critical Care Medicine, University of Bonn, Bonn, Germany*
[2]*Staff Anaesthetist, Palo Alto VA Health Care System, Associate Professor of Anesthesia, Stanford University School of Medicine, Stanford, California, USA*

References

1 Lerou JG, Dirksen R, Beneken Kolmer HH, Booij LH. A system model for closed-circuit inhalation anesthesia. I. Computer study. *Anesthesiology* 1991, **75**(2): 345–55
2 Lerou JG, Dirksen R, Beneken Kolmer HH, Booij LH, Borm GF. A system model for closed-circuit inhalation anesthesia. II. Clinical validation. *Anesthesiology* 1991; **75**(2): 230–7
3 Rietbrock S, Wissing H, Kuhn I, Fuhr U. Pharmacokinetics of inhaled anaesthetics in a clinical setting: description of a novel method based on routine monitoring data. *Br J Anaesth* 2000, **84**: 437–42
4 Wissing H, Kuhn I, Rietbrock S, Fuhr U. Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; **84**· 443–9
5 Dean JM. GasMan. *MD Comput* 1986; **3**(3): 537

British Journal of Anaesthesia **84** (4): 432–3 (2000)

Editorial II

Assessment of clinical competence

The most common way of assessing competence at the undergraduate and postgraduate levels in the UK has been the traditional clinical viva. In an era where the quality of assessments, in terms of validity and reliability, is under increasing scrutiny, this approach has come under mounting criticism. Evidence demonstrating the unreliability of the traditional clinical examination was published in North America in the 1960s but seems to have had little impact on assessment practices in the UK and countries with similar medical education and training systems. This can partly be explained by the lack of any obvious alternatives.

The last 20 years have seen some dramatic changes in research and development in methods of assessment.[1] For example, the advent of the Objective Structured Clinical Examination (OSCE) has provided a viable alternative to the traditional approach and has become increasingly popular, particularly at the undergraduate level.[2] The OSCE has mutated into many versions, ranging from the classic form of multiple short (5–10 min) stations involving examiners rating candidates on a structured marking sheet, through to multiple long stations (30 min) involving candidates undertaking a full clinical assessment on simulated patients trained to score the performance. An example of the latter is the new Clinical Skills Assessment being used by the Educational Commission for Foreign Medical Graduates in the USA.[3]

Research on multistation examinations has produced valuable technical data which provide us with evidence about how to design such tests to achieve high levels of reliability[4] and guidelines on how to construct them to demonstrate acceptable validity.[5] However, valuable as they are for certification purposes, they do not provide a panacea and some important components of clinical competence are not readily or even appropriately assessed under examination conditions. These include attributes in many areas involving in-depth interaction between the student or doctor and patients, relatives, colleagues or others and where attitudes and ethical considerations play a major part in determining performance. Such areas inevitably require assessment in more complex situations and over an extended period of time in the workplace. Unfortunately, the methodology available to undertake assessment of these vital components is far less well developed and likely to be prone to problems of unreliability, perhaps even more so than the traditional clinical examination.

The article by Greaves and Grant in this issue[6] examines some of the matters relating to the in-service assessment of anaesthetic trainees. The authors point out that measures of clinical outcome are not suitable for this task as they are often influenced by many factors unrelated to the performance of the doctor. They believe that the well accepted approach of observing clinical practice must be an important facet of the assessment of competence. They set out to investigate how this is currently undertaken and how it might be made more standardized without losing the flexibility of the present approach to evaluate the integration of technical, professional and judgemental skills into an overall performance. The results are the outcome of focus group discussions involving a panel of consultant and trainee anaesthetists. They identified the approaches used by supervisors of training (interrogation, documentary evidence, observation). However, how they organized the information and used it to judge performance seemed less clear. Nevertheless, consultants seemed confident that the assessment they made was valid and reliable. Unfortunately, no evidence that this is the case is provided and past experience would suggest that this confidence might not be well founded. On the other hand, the consultants did recognize the value of multiple observations by different observers as a requirement to enhance reliability and fairness. What was interesting was a recognition that certain patterns of behaviour might be more critical in recognizing incompetence; these included lack of flexibility, failure to adapt to changing circumstances, irrational judgements and a disordered approach. The outcome of the study included a definition of attributes of competent practice with associated statements of appropriate and inappropriate behaviours. This was linked to a more systematic strategy for assessment than would currently be the case. The authors conclude by pointing out that such a process needs to be tested on large numbers of trainees in order to establish levels of validity and reliability.

Such studies are an important first step in the development of improved methods of performance-based rather than competence-based assessments. The requirements of the recent changes to specialist training and the advent of 'revalidation' highlight the need for more defensible approaches to assessing performance in practice. Currently only limited research is available to guide progress but experience from competence-based testing alerts us to the fact that solutions will be more complex and more expensive (in time). We will have to rely on the judgement of peers making direct observations, a process that will enhance validity if appropriately

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

structured and targeted but which will inevitably cause problems with reliability. The latter concern will require the development of tools to guide the process and record the outcome as well as necessitate the training of assessors. However, these will have limited impact and, for high-stakes summative purposes, it will be necessary to combine the assessments from multiple observers over many instances or periods of practice.

D. I. Newble
Department of Medical Education
University of Sheffield
Coleridge House
Northern General Hospital
Sheffield S5 7AU
UK

References

1 Newble D, Jolly B, Wakeford R, eds. *The Certification and Recertification of Doctors: Issues in the Assessment of Clinical Competence.* Cambridge: Cambridge University Press; 1994.
2 Harden RM, Gleeson FA. Assessment of clinical competence using an objective structured clinical examination (OSCE). *Med Educ* 1979; **13**; 41–54
3 Whelan G. Educational Commission for Foreign Medical Graduates: clinical skills assessment prototype. *Med Teacher* 1999; **2**: 156–60
4 Newble DI, Swanson DB. Psychometric characteristics of the objective structured clinical examination. *Med Educ* 1988; **22**: 325–34
5 Newble D, Dawson BT, *et al.* Guidelines for assessing clinical competence. *Teaching and Learning in Medicine* 1994; **6**; 213–20
6 Greaves JD, Grant J. Watching anaesthetists work: using the consultant's professional judgement to assess the trainee's developing clinical competence. *Br J Anaesth* 2000; **84**: 525–33

British Journal of Anaesthesia 84 (4). 434–6 (2000)

Editorial III

2000 – Time to apply Occam's razor to failure of hypoxic pulmonary vasoconstriction during one lung ventilation

The matching of ventilation with perfusion has a particular relevance to thoracic anaesthetists because of the unique circumstances that arise as a consequence of implementing one lung ventilation (OLV) – their stock-in-trade. It is to be expected that a significant proportion of cardiac output will continue to perfuse the non-ventilated lung. A major cause of debate relates to observations that this is rarely as much as 50% and usually, under experimental circumstances, closer to 25%.[1] The operation of passive (mechanical) and active (biological) forces are suggested for the smaller than anticipated shunt fraction. The most elusive to demonstrate is hypoxic pulmonary vasoconstriction (HPV). HPV is regarded as a primary and homeostatic mechanism that assures perfusion is matched to ventilation in the normal subject. It invokes a sensing system within the lung that detects the presence of a hypoxic gas mixture or, perhaps, blood oxygen content and reflexly activates a vasoconstrictive response that regulates the blood flow to poorly ventilated alveoli or lung zones. It developed a piquancy for thoracic anaesthetic practice when it was shown that the potent inhalational agents of the day instituted its failure and could contribute to hypoxaemia.[1–3]

Translating the diverse and unphysiological animal experiments to man proved equivocal, particularly in the arena of clinical practice.[1 4] Attempts to do so are prefaced by major and unrealistic assumptions about the conduct of anaesthesia.[5] Tests to measure shunt fraction have global end-points and are not sensitive enough to discriminate the actual contribution from non-ventilated lung. It was argued that the responses to pharmacological agents in populations undergoing pulmonary resection were masked by obtrusive circumstances such as the changes to cardiac output consequent on perioperative and surgical events and confounding variables of pulmonary pathology.[6] Studies were with small numbers and not conducted on uniform cohorts of right or left hemithorax operations: a bias or type error due to the normal or larger size of the right lung, and hence greater perfusion, is just one concern about the statistics. The failure of HPV caused by potent inhalational agents appeared to contribute 4–5% of the shunt fraction[5] – a level that is clinically marginal and, arguably, biologically insignificant.

By the end of the 1980s, two of the main exponents in the field[7 8] appeared to agree that HPV had less significance for OLV than previously thought. Though viewed as academically important, the issues raised were regarded as unlikely to have any clinical impact.[5] By increasing the inspired oxygen concentration and changing the ventilation pattern, putatively deleterious effects on oxygenation were easily, safely and non-specifically remedied, without greatly impeding surgical access.

However, even now, with clinical reports that the shunt fraction to the non-ventilated lung is 35–45% with techniques considered to have only a small influence on HPV,[9–11] the concept of failure of HPV continues to impact and exercises an undue influence on trainees and examination candidates. If asked to rank the causes of hypoxia during OLV, trainees put failure of HPV, due to the presence of a potent inhalational agent, second to perfusion of the non-ventilated lung on the list of importance and size of contribution to the shunt. Common and remediable causes, such as the position of the double lumen endobronchial tube, sub-optimal ventilation of the dependent lung, and the effects of the activities of the surgeons, are excluded. This distraction by side issues related to the non-ventilated lung, means that most learners actively need to be taught that a far more significant contribution to the size of the shunt is made by the forces of the anaesthetic and surgical processes on the functional residual capacity (FRC) of the lung being used to maintain life. In clinical practice, these all result in hypoventilation of the lung undergoing OLV and are only realistically reversible by the single force of effective ventilation via the long and narrow conduit – paediatric in dimensions – that is the bronchial lumen of standard double lumen tubes. Occam's razor, so-called after a 14th century monk, William of Ockham, is a tool of logic and philosophy that is used for rationalizing scientific debate by paring the hypothetical. Most commonly translated as 'entities must not be multiplied beyond necessity', it is used to argue that of two or more explanations for a phenomenon, the simplest is the most likely to be true. In context, the questions therefore posed are – is there an alternative significant determinant of perfusion of the ventilated lung that is operational on the institution of OLV, and is it the more likely mechanism? Certainly to practitioners, the earlier explanations,[12–14] and what is more, effectively the visible ones, are more persuasive than speculation on an intrinsic oxygen sensor system that can be stunned in animals by potent inhalational anaesthetics. The counter-argument goes, that with the onset of surgery the main determinants of preferential flow to the ventilated, dependent lung are passive (mechanical) namely: the effects of the open or artificial pneumothorax and absorption atelectasis on the pulmonary vascular resistance of non-ventilated (and often, in practice – pathology containing) lung; and a gravitational effect on blood flow on adoption

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

of the lateral decubitus position in those undergoing thoracotomy.

The debate between the chimerical and the visible was healthy for science and clinical practice so long as it was kept in a perspective that did not result in harm to patients. The focus of trainees on the hypothetical is of concern to the teachers and supervisors because remediable conditions can remain undetected and treatment unlearnt. Reversible pathophysiology, such as a collapsed lobe as a result of slight movement of a tracheal tube, may go unnoticed with longer term consequences for morbidity; poor technique may be encouraged. However, the potential to cause patients harm during anaesthesia is remote as the conduct of and selection for OLV nowadays is better: hypoxaemia is easily spotted and readily corrected.

But the arguments have gone beyond being between academic and journeyman. A fundamental axiom of the use of OLV – that it is never so essential that risks should be taken with a patient's life to achieve it – has been breached. It has become necessary to apply a brake of some sort and, hopefully, a 14th century one may be all that is needed.

A vogue for attempting to manipulate pulmonary perfusion has followed on from the discoveries about natural and specific vasoactivators such as nitric oxide.[15 16] Legitimately, and increasingly, this has been followed for the management of acute respiratory distress syndrome and allied conditions. The techniques and agents are not without hazard. Some of the new generation of drugs which are being considered for use to counter the effects of anaesthesia on HPV mechanics during OLV are very toxic[17] and have been used on patients undergoing routine thoracic surgery.[15] The juggling of pulmonary vasodilators and constrictors during OLV in man is of dubious logic. It is mere tinkering of a complex and ill-understood pathophysiological process and reaps a paltry and even dangerous return on shunt fraction.[18] It is only justified in exceptional circumstances during anaesthesia in those undergoing surgery for respiratory failure.[19]

Fundamentally, and trite though it may seem, in the routine of thoracic anaesthesia practice there is no good physiological reason why oxygen is not the ideal or the ethical treatment for hypoxaemia. Increasing the inspired oxygen concentration and optimizing dependent lung FRC by manipulating the frequency, tidal volumes, inspiratory and expiratory phases of ventilation and the application of PEEP, are perfectly good actions that have proved convenient, adequate and safe for the majority of cases. If particular regard is made to ensure that ventilation strategies account for the paediatric dimensions of the single lumens of double lumen tubes then, in practice and in the last resort, partial recruitment of the non-ventilated lung is required only occasionally. It is cheap, safe and curative, and rarely anything but a slight and easily overcome inconvenience for the skilled surgeon. That it is such an infrequent requirement, and that first line actions usually are corrective, point to the thesis that the mechansims that make the shunt fraction reach a critical level during OLV relate to hypoventilation of ventilated lung rather than diversion of perfusion to non-ventilated lung.

Periodically, those charged with overseeing and those considering conducting clinical advances need direction from the practitioners in the field to help define standards. The change of millennium is an appropriate time to review guidelines for ethical research.[20] It is also an appropriate time to take stock of HPV, its relevance and the vexed questions that the concept of its failure has raised for nigh on 30 yr. But, the debates must be returned to an academic framework. No further risk, such as exposure to toxic drugs, should be borne by those whose care is entrusted to us. In this instance, applying Occam's razor will create the logic for a moratorium to be put on studies that have a high potential to be harmful and are therapeutically unjustified. Failure of HPV is cast as a doubtful clinical entity: certainly, it does not require a specific therapy. Without any *raison d'etre*, the intent to test novel and experimental therapies and/or introduce them to the routine of thoracic anaesthetic practice can, and should, be declared unethical.

I. D. Conacher
Department of Cardiothoracic Anaesthesia
Freeman Hospital
Newcastle upon Tyne NE7 7DN
UK

References

1 Benumof JL. One lung ventilation and hypoxic pulmonary vasoconstriction. *Anesth Analg* 1985; **64**: 821–33

2 Sykes MK, Arnot RN, Jastrzebski J, Gibbs JM, Obdrzalek J, Hurtig JB. Reduction of hypoxic pulmonary vasoconstriction in the dog during trichlorethylene anaesthesia. *J Appl Phys* 1975; **39**: 103–9

3 Marshall C, Lindgren L, Marshall BE. Effects of halothane, enflurane and isoflurane on hypoxic pulmonary vasoconstriction in rat lungs *in vitro*. *Anesthesiology* 1984; **60**: 304–8

4 Carlsson AJ, Bindslev L, Santesson J, Gottlieb I, Hedenstierna G. Hypoxic pulmonary vasoconstriction in the human lung: the effect of prolonged unilateral hypoxic challenge during anaesthesia. *Acta Anaesth Scand* 1985; **29**: 346–51

5 Benumof JL, Augustine SD, Gibbons JA. Halothane and isoflurane only slightly impair arterial oxygenation during one lung ventilation in patients undergoing thoracotomy. *Anesthesiology* 1987; **67**: 910–15

6 Marshall BE, Marshall C. Continuity of response to hypoxic pulmonary vasoconstriction *J Appl Phys* 1980; **59**: 189–96

7 Marshall BE. Anaesthesia for one-lung ventilation. *Anesthesiology* 1988; **69**: 630

8 Benumof JL. Anesthesia for one-lung ventilation. *Anesthesiology* 1988, **69**: 631

9 Slinger P, Scott WAC. Arterial oxygenation during one lung ventilation. a comparison of enflurane and isoflurane *Anesthesiology* 1995; **82**: 940–6

10 Reid CW, Slinger PD, Lenis SA. A comparison of the effects of propofol-alfentanil versus isoflurane anesthesia on arterial oxygenation during one lung ventilation. *J Cardiothorac Vasc Anesth* 1996, **10**: 860–3

11 Wang JYY, Russell GN, Page RD, Jackson M, Pennefather SH. Comparison of the effects of sevoflurane and isoflurane on arterial oxygenation during one lung ventilation. *Br J Anaesth* 1998; **81**: 850–3

12 Gaensler EA. In Newman RW, Finer GE, Downs JE. The routine use of Carlens double-lumen endobronchial catheter. *J Thor Cardiovasc Surg* 1962; **43**: 339

13 Rigg JRA. Pulmonary atelectasis after anaesthesia: pathophysiology and management. *Can Anaesth Soc J* 1981; **28**: 305–13

14 Werner O, Malkvist G, Beckman A, Stahle S, Nordstrom L. Carbon dioxide elimination from each lung during endobronchial anaesthesia. *Br J Anaesth* 1984; **56**: 995–1001

15 Eisenkraft JB. Hypoxic pulmonary vasoconstriction. *Curr Op Anesthesiol* 1999; **12**: 43–8

16 Payen DM, Muret J. Nitric oxide and almitrine: the definitive answer for hypoxaemia. *Curr Op Anesthesiol* 1999; **12**: 37–42

17 Moutafis M, Liu N, Dalibon N, Kuhlman G; Ducros L, Castelain MH, Fischler M. The effects of inhaled nitric oxide and its combination with intravenous almitrine on PaO_2 during one lung ventilation in patients undergoing thoracoscopic procedures. *Anesth Analg* 1997; **85**: 1130–5

18 Ismail-Zade IA, Vuylsteke A, Ghosh S, Latimer RD. Inhaled nitric oxide and one-lung ventilation in the lateral decubitus position (Letter). *J Cardiothorac Vasc Anesth* 1997; **11**: 926–7

19 Conacher ID. Dynamic hyperinflation – the anaesthetist applying a tourniquet to the right heart. *Br J Anaesth* 1998; **81**: 116–7

20 Gilbertson AA. Ethical review of research. *Br J Anaesth* 1999; **82**: 6–7

British Journal of Anaesthesia 84 (4): 437–42 (2000)

BJA

CLINICAL INVESTIGATIONS

Pharmacokinetics of inhaled anaesthetics in a clinical setting: description of a novel method based on routine monitoring data†

S. Rietbrock[1], H. Wissing[2], I. Kuhn[2] and U. Fuhr[1]*

[1]*Institute for Pharmacology, Clinical Pharmacology, University of Köln, Gleueler Strasse 24, D-50931 Köln, Germany.* [2]*Department of Anaesthesiology, Johann Wolfgang Goethe University Hospital, Theodor-Stern-Kai 7, D-60950 Frankfurt/Main, Germany*

**Corresponding author*

Pharmacokinetic parameters of inhaled anaesthetics have previously been assessed experimentally in healthy volunteers. In contrast, we developed a method to estimate pharmacokinetic parameters under clinical conditions. We obtained data from the continuous routine monitoring of fractional concentration and ventilation during anaesthesia with desflurane, isoflurane and sevoflurane. By simulation studies, we assessed the effects of several sources of variation, including the noise of measurement, the second gas effect and rounding errors or a limited number of displayed digits. Stable fits to a two-compartment model were obtained for both real and simulated data sets in all cases. The most stable parameter was the intercompartmental clearance, and the most sensitive parameter was the volume of distribution. The bias in pharmacokinetic parameters caused by adding errors to measured concentrations was similar for the different compounds. We conclude that the model allows the estimation of an alternative set of pharmacokinetic parameters that can reliably describe the behaviour of volatile anaesthetics under clinical conditions, and allow comparison between agents.

Br J Anaesth 2000: **84**; 437–42

Keywords: anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane; anaesthetics volatile, desflurane; pharmacokinetics, models

Accepted for publication: October 12, 1999

The pharmacokinetics of inhaled anaesthetics has been assessed in experimental settings in healthy volunteers. Previous studies obtained classical wash-in and wash-out curves from step changes of the inspired partial pressure of the anaesthetic.[1–3] These curves are easily analysed, even with graphical methods. to give different time constants representing different virtual volumes of distribution. Blood or expired vapour partial pressures in these studies were determined by gas chromatography. Samples from the blood or the expired gas were taken first at frequent intervals (1–3 min), and subsequently less frequently. During wash-out, samples were drawn for up to several days after drug administration, allowing the construction of pharmacokinetic models with up to four or five compartments.[1–3]

These experimental conditions are not easily transferred to clinical anaesthesia, when volatile anaesthetic partial pressure is increased or decreased in relation to the surgical stimulus. The variable inspired and end-tidal partial pressure of the compound under investigation makes pharmacokinetic variables difficult to assess. As pharmacokinetic parameters vary between subjects, an adequate number of subjects must be investigated in order to obtain reliable mean values. For the comparison of different compounds, intraindividual variation must also be considered. One of the merits of a purely experimental approach, with simultaneous administration of several anaesthetics, is that intraindividual variability is minimized. However, for ethical and cost reasons, only a few subjects were tested in such studies.[2 3]

In the present investigation, we examined an alternative approach. In current anaesthetic workstations, ventilatory variables as well as the inspired and end-tidal anaesthetic concentrations are measured continuously and recorded frequently. Therefore, from a formal point of view, the input function ($x_1(t)$) and the system response (output function, $x_0(t)$) of the pharmacokinetic system under investi-

---

†This article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

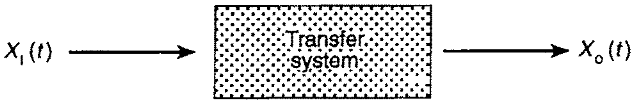


Fig 1 Scheme of the transfer system The input function $x_i(t)$ is represented by the time course of F_I and the uptake, the system response $x_o(t)$ by the time course of F_E. The transfer function $G(t)$ can be determined when the time course of the input and the output function are known.

gation is recorded almost continuously, so that we can determine the characteristics of the transfer system. Figure 1 illustrates the formal description of the transfer system. As a function *vs* time it is described by pharmacokinetic parameters. Pharmacokinetic methods can be used to describe the transfer function and to determine the implicit differential equations.

We set out to develop and describe a method that can derive pharmacokinetic parameters for inhaled anaesthetics from routine data in patients, and to assess the stability of the parameter estimates obtained. We used clinical data for the entire period of anaesthesia from intubation to extubation to establish a two-compartment model and to estimate pharmacokinetic parameters. We found distinct differences between desflurane, isoflurane and sevoflurane other than differences that could be attributed to their physicochemical properties.[4–7]

Methods

Acquisition of experimental data

Data from low-flow anaesthesia in 48 patients receiving desflurane, isoflurane or sevoflurane (16 patients for each anaesthetic) were used. Mean duration of anaesthesia was 111 (SD 44) min for desflurane, 148 (41) min for isoflurane and 115 (57) min for sevoflurane. Details of anaesthesia are described in the accompanying paper.[4] The concentrations of these compounds and the ventilation data provided by the monitoring system of the Ohmeda Modulus CD/CV were recorded at 20-s intervals using the integrated floppy disk drive. Alveolar ventilation ($\dot{V}_{alv}$) was estimated from the expiratorily measured tidal volume (V_T) less a dead space of 2.0 ml per kg body weight, corresponding to 25% of the set tidal volume.[8]

After calibration, the accuracy of the internal gas analyser of the Ohmeda Modulus CD/CV was assessed using mixtures of calibration vapour and ambient air. In the range from 0 to 1.1 vol% isoflurane the variation was less than ±0.5 of the least significant digit. The accuracy was the same after 6 h of continuous working and after 1 week.

A modified Ohmeda Miniabsorber System circle system was used which did not influence the measured inspiratory concentration.[9] The accuracy of the turbine volumeter was measured by ventilating an adiabatic test lung. Variation was less than ±5% throughout the operating range.

Estimation of parameters

Based on the direct relationship between the volume of a gas and its molar mass, pharmacokinetic parameters were derived from the inspired and end-expired vapour concentration *vs* time and alveolar ventilation using a two-compartment model. The central compartment includes the lung and very rapidly equilibrating tissues (not anatomically defined); the peripheral compartment is the rest of the body. The data were also assessed using a corresponding three-compartment model, but this gave stable results in only 50% of data sets and is therefore not described further.

The following pharmacokinetic parameters were derived from inspired and end-expired concentration values and alveolar ventilation: volume of distribution in the central compartment, V_1; intercompartmental clearance, CL_{12}, measuring transport into the periphery; and microconstant, k_{21}, for transit from the periphery. To this end, a two-compartment model was applied to describe changes of expired concentrations (equation 1) and concentration in the peripheral compartment (equation 2) for inhaled anaesthetics with time:

$$\frac{d}{dt} V_1F_1 = -k_{12}F_1V_1 + k_{21}F_2V_2 - \dot{V}_{alv}F_1 + \dot{V}_{alv}F_1 \quad (1)$$

$$\frac{d}{dt} V_2F_2 = k_{12}F_1V_1 - k_{21}F_2V_2 \quad (2)$$

V_1 and V_2 denote the central and peripheral volume of distribution respectively, k_{12} and k_{21} the microconstants, F_1 and F_2 the fraction of anaesthetic vapour in the central and peripheral compartments respectively, and $\dot{V}_{alv}$ the alveolar ventilation. Because the system assumes that the central volume of distribution is well stirred, F_1 is assumed to equal the fraction of anaesthetic in the end-expired gas, F_E'. Thus, F_E' is used subsequently in place of F_1. In addition, the uptake of volatile anaesthetic $U(t)$ can be expressed as

$$U(t) = \dot{V}_{alv}(F_1 - F_E') \quad (3)$$

The following equation was used for the calculation of intercompartmental or transport clearance CL_{12}:

$$CL_{12} = k_{12}V_1 = k_{21}V_2 \quad (4)$$

Based upon this definition, equations (1) and (2) become

$$\frac{d}{dt} V_1F_E = -CL_{12}F_E' + CL_{12}F_2 + U(t) \quad (5)$$

$$\frac{d}{dt} V_2F_2 = -CL_{12}F_E' - CL_{12}F_2 \quad (6)$$

Solving for F_E' and F_2 yields

$$\frac{d}{dt} F_E' = -\frac{CL_{12}}{V_1} F_E' + \frac{CL_{12}}{V_1} F_2 + \frac{U(t)}{V_1} \quad (7)$$

$$\frac{d}{dt} F_2 = \frac{CL_{12}}{V_2} F_E' - \frac{CL_{12}}{V_2} F_2 \quad (8)$$

The microconstant k_{21} can be interpreted as the inverse of the transit time in the periphery. Subsequently, we used V_1, CL_{12} and k_{21} to characterize the two-compartment model.

The solution of the differential equation can be obtained by solving the two-compartment model with zero order absorption for each sampling interval after algebraic manipulation of the uptake term. The differential equations were solved explicitly for each sampling interval to obtain the calculated expired fractional concentration, $F_E'_{,calc}$. $F_E'_{,calc}$ was then fitted to the observed values by the least squares method based on the simplex algorithm.[10] An additive error model was assumed because the rounding errors of the recorded concentrations are absolute errors.

Simulation studies

We assessed the robustness of the parameter estimates. These estimates may be influenced by factors such as measurement noise, changes in carbon dioxide, oxygen and water concentrations in the measured volumes, the second gas effect,[11–14] rounding errors of the measurement device, and a limited number of displayed digits. In the pharmacokinetic system, measurement noise is present in the input and output variables. Because of subsequent calculation of end-expired concentrations, the second gas effect, mimicking an increase in ventilation, may be important at the start of anaesthesia. It can be simulated by an artificial increase in uptake. The loss of precision as a result of rounding errors by the measurement device may be assessed by normally distributed random replications.

Thus, the effect of the presumed confounding factors can be assessed from the dependence of the curve fit on random and/or systematic error of the input signal, on the sampling rate and on random error of the output signal.

In the following simulation studies using published routines,[10] we made worst-case assumptions about the magnitude of the error that could confound the estimation of the pharmacokinetic parameters.

Study A: random error of the input signal

To consider this uncertainty in the uptake $U(t)$, the input variables F_I and $\dot{V}_{alv}$ were disturbed simultaneously by independent log-normally distributed random noise. A standard deviation of $\sigma=0.1$ was used to simulate arbitrary non-specific noise causing 10% variation in both input variables, and $\sigma=0.025$ was applied to assess the 2.5% increase in variation expected by the round-off error at a concentration of 1–10 vol% when two digits were available.

Study B: systematic bias combined with round-off error of the input signal

For the initial 10 min the uptake was increased by a factor of 1.2 to simulate an initial second gas effect. For the round-off error of the uptake, $\sigma=0.025$ was assumed, as in study A.

Study C: decreased sampling rate

The sampling rate was diminished by factors of 2, 3 and 4 to determine its influence.

Study D: random error of the output signal

The sampled expiratory concentrations were distorted by log-normally distributed random noise ($\sigma=0.1$).

In all cases, simulation was based on the 16 measured time courses of desflurane, isoflurane and sevoflurane anaesthesia.[4] When random errors were applied (in studies A, B and D), 20 data sets were generated based on each of the measured time courses. From these simulated data sets, pharmacokinetic parameters were estimated as described above. The mean difference between the model parameters determined from the measured time courses and those determined from the perturbed time courses was defined as bias. The mean coefficient of variation of the parameters estimated from artificially perturbed time courses was defined as scatter.

Results

Goodness of fit

Stable fits were achieved with the two-compartment model described for both real and simulated data sets in all cases. The average (SD) of the root mean square errors for $F_E'_{,calc}$ were 0.16 (0.04) (max. 0.21) vol% for desflurane, 0.05 (0.01) (max. 0.07) vol% for isoflurane and 0.05 (0.01) (max. 0.08) vol% for sevoflurane in real data sets, while measured expiratory concentrations reached 9.5 vol% for desflurane, 1.5 vol% for isoflurane and 3.4 vol% for sevoflurane.

In no case did the individual plots of residuals *vs* time and estimated *vs* measured concentration show that the model was incorrect. To illustrate the goodness of fit for each of the volatile anaesthetics, the residuals of the data sets with the highest mean square errors are shown in Figure 2.

The results from the original data sets are reported in the accompanying paper.[4]

Robustness of parameter estimates

The bias and scatter for the parameters V_c, CL_{12} and k_{21} are shown in Tables 1, 2 and 3 respectively. The scatter reflects the introduced error in all cases. The most stable parameter was the intercompartmental clearance. The volume of distribution was more dependent on the magnitude of error than the remaining parameters. The data with 20% initial systematic error, simulating a second gas effect, gave the largest bias; visual examination of the residual plots shows a slightly impaired fit for the first 10 min. The effect of variation in the input value was considerably more pronounced than that of the output value. A reduction of the sampling rate to 1/4 changed the estimated volume of distribution by up to 43% (mean), whereas the other parameters were not changed by more than 15% (mean). The impact of the error introduced in the parameter estimates was similar for the different inhaled anaesthetics, although isoflurane, the compound with the largest time constants,

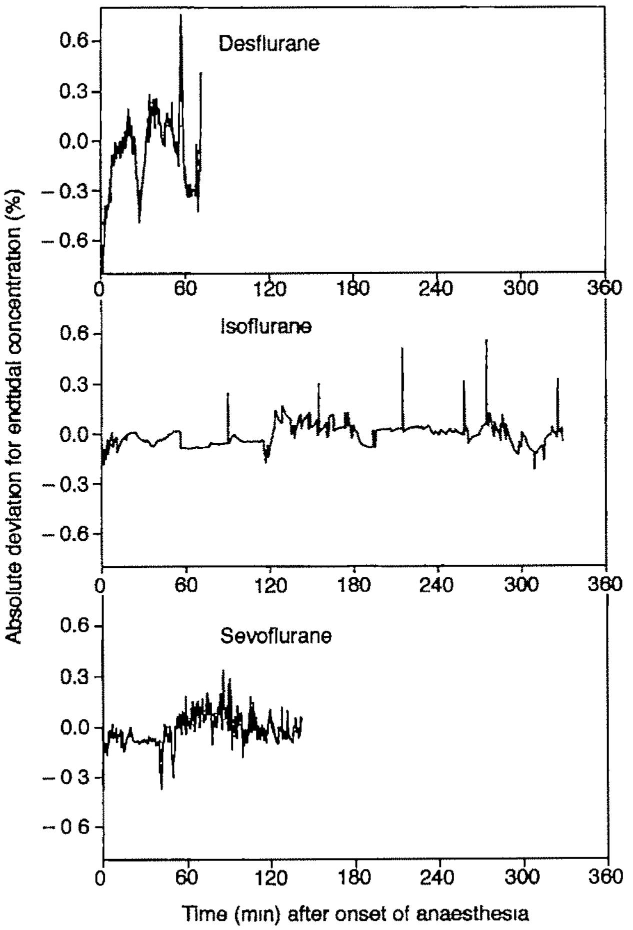


Fig 2 Residuals *vs* time during desflurane, isoflurane and sevoflurane anaesthesia for the data sets with the poorest fits. Mean F_E for the whole course of anaesthesia in these cases was 5.1, 0.9 and 1.5 vol% for desflurane, isoflurane and sevoflurane respectively The deviation 'spikes' in the isoflurane course were caused by invalid data from the gas analyser during calibration not eliminated in the referenced raw data set.

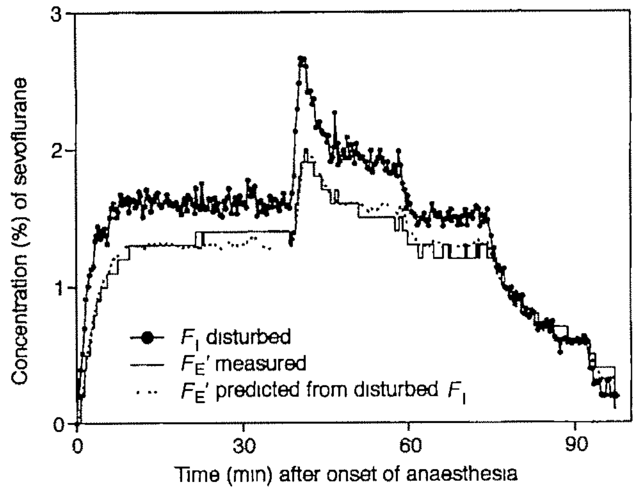


Fig 3 Concentration *vs* time profile during sevoflurane anaesthesia in a representative patient for whom a steep concentration change was necessary. F_I was disturbed by a systematic 20% bias during the first 10 min and random noise during the whole sampling period with $\sigma = 0.025$ (see Study B in Methods). An excellent fit was possible with a two-compartment model even during the concentration change, despite the error introduced.

was somewhat less affected than the other compounds. An individual time profile with a steep concentration change for sevoflurane, including the fitted curve obtained with perturbation, is shown in Figure 3.

Discussion

This method for the determination of the pharmacokinetics of volatile anaesthetics using routine clinical data should have advantages compared with experimental measurements.[1-3] These include the number of patients that may be investigated, the frequency of sampling, the fact that it is non-invasive and that it takes into account possible feedback of physiological effects of the individual agent on its own pharmacokinetic properties, and the lower cost of measurement. However, these advantages may be unimportant if the estimation of parameters by this method is subject to important bias. Therefore, we required a model with the following properties:

- The model should be as simple as possible since otherwise parameter estimation might become unstable;
- The model should incorporate transport to a peripheral compartment;
- The method should not be affected by systematic and random errors.

In this study, we applied the least squares method using the end-expired fractional concentration as the dependent variable. This is because standard maximum likelihood methods comprising the statistical error of the dose administered would yield a large covariance matrix, which cannot be inverted by standard methods within a reasonable computing time. The maximum likelihood procedure is based on the parameterised distribution of the observed values and selects those parameters with the largest likelihood for the observed values. If these are uncorrelated and normally distributed, the maximum likelihood approach coincides with the least squares method.[15]

Quality of fit can be quantified using the root mean square error. As its values were small compared with the measured concentrations, estimated values for F_E' in general described the measured data very precisely. In addition, the root mean square errors of the data sets with the poorest fit exceeded the mean values by not more than 1.6-fold, showing that the model used was satisfactory in all cases. Even for these data sets, the residuals *vs* time plots do not suggest misspecification of the model (Fig. 2). The observation that the root mean square errors were within the magnitude of rounding errors suggests that improving the fit by the use of more complex models is not generally feasible. This is supported by the finding that stable estimates of pharmacokinetic parameters for a three-compartment model could not be obtained in 50% of the data sets,

Table 1 Effect of data set modification on estimated volume of distribution in the central compartment (V_1). *See Methods; †per cent of unperturbed value, ‡coefficient of variation of perturbed values

Type of simulation*	Modification of data sets	Desflurane		Isoflurane		Sevoflurane	
		Bias† %	Scatter‡ %	Bias %	Scatter %	Bias %	Scatter %
A	10% variation in input variables	23±10	8±2	14±7	8±2	30±11	10±1
A	2.5% variation in input variables	2±1	2±1	1±1	2±0	3±2	3±1
B	Initial error plus 2.5% variation in input variables	79±20	4±1	67±19	3±1	83±27	5±1
C	1/2 sampling rate	17±8	–	4±8	–	12±9	–
C	1/3 sampling rate	33±13	–	13±11	–	24±14	–
C	1/4 sampling rate	43±15	–	13±15	–	29±22	–
D	10% variation in output	0±2	9±3	0±3	9±2	–1±4	13±4

Table 2 Effect of data set modification on estimated intercompartmental clearance from the central to the peripheral compartment (CL_{12}) *See Methods, †per cent of unperturbed value, ‡coefficient of variation of perturbed values

Type of simulation*	Modification of data sets	Desflurane		Isoflurane		Sevoflurane	
		Bias† %	Scatter‡ %	Bias %	Scatter %	Bias %	Scatter %
A	10% variation in input variables	0±1	9±4	0±1	3±1	1±3	6±2
A	2.5% variation in input variables	0±4	2±1	0±1	1±0	0±0	2±1
B	Initial error plus 2.5% variation in input variables	25±29	3±2	4±9	1±0	7±11	2±1
C	1/2 sampling rate	–6±8	–	0±2	–	–1±2	–
C	1/3 sampling rate	–15±21	–	–2±2	–	–2±2	–
C	1/4 sampling rate	–7±28	–	–2±5	–	–2±4	–
D	10% variation in output	0±2	9±3	–1±1	3±1	–1±1	6±2

Table 3 Effect of data set modification on estimated time constant for transit from the peripheral to the central compartment (k_{21}). *See Methods; †per cent of unperturbed value; ‡coefficient of variation of perturbed values

Type of simulation*	Modification of data sets	Desflurane		Isoflurane		Sevoflurane	
		Bias† %	Scatter‡ %	Bias %	Scatter %	Bias %	Scatter %
A	10% variation in input variables	–17±8	9±4	–5±2	4±2	–16±6	11±6
A	2.5% variation in input variables	–2±1	2±1	0±0	1±1	–1±1	3±2
B	Initial error plus 2.5% variation in input variables	–15±16	3±2	–11±12	1±1	–22±28	3±2
C	1/2 sampling rate	–6±8	–	2±5	–	–1±4	–
C	1/3 sampling rate	–15±22	–	1±10	–	–4±6	–
C	1/4 sampling rate	–7±28	–	3±8	–	1±10	–
D	10% variation in output	0±2	9±3	–11±12	1±1	–1±1	6±1

and that multicompartment models such as those derived experimentally[1–3] were not appropriate. It therefore appears that during clinical anaesthesia under the conditions examined here, slow transport processes to a third compartment are of minor importance, and to a fourth or fifth compartment are not relevant to the concentration in the central compartment.

The random error used in the simulation studies to disturb input and output variables represents the round-off error and the uncertainty of the measurement. The round-off error accounts for not more than 2.5% when two digits are available and the fractional concentration is in the range of 1–10 vol% (for 1.0 vol%, maximal round-off error is 0.05= 5%, and minimal round-off error is zero, giving a mean error of 2.5%). Since the accuracy of the measurement was better than the round-off error, it is supposed that the overall random error is closer to 2.5 than to 10%. Other sources of error include the effects on inspired and expired measurements of volumes and concentrations of inhaled agents caused by changes in carbon dioxide, oxygen and water concentrations. No corrections were made for water vapour and respiratory quotient; however, they are included, at least in part, in the procedure used to estimate alveolar dead space.[8] The error caused by these factors should be less than 5%, taking the compliance of the system and condensation of water in the expiratory limb into account. For a simulated 2.5% error in the input variables, the bias of all pharmacokinetic parameters was negligible (Tables 1–3). A presumed 10% error (well above true error of measurement) caused important changes, mainly for the volume of distribution, only when applied to the input variables. In summary, it appears that the expected sources of inaccuracy have no major impact on the results.

The second gas effect caused by nitrous oxide ventilation[12] was presumably overestimated in early studies.[13] When applying the square root law for nitrous oxide postulated by Severinghaus[14] (N_2O uptake = $1000/\sqrt{t(\text{min})}$), the mean excess ventilation is estimated as 630 ml within the first 10 min of anaesthesia. Although the true second gas effect is expected to be considerably lower,[11 13] it is less than our assumption of an initial systematic error of 20%. Therefore, we expect that the bias in the central volume of distribution introduced by a possible second gas effect is less than 40% and has little effect on the other parameters.

Contamination of F_E' by F_I from parallel dead space was not taken into account by our model. We expect that this contamination is negligible, as we applied concentration changes in a low-flow circle system, and these changes are slower than those that occur with step-like changes in a non-rebreathing system.

Because of the continuous and variable input of drug into the system, a high sampling rate is essential for the correct description of the dose. The observation that the calculated volume of distribution was affected only if the sampling rate was reduced by more than a factor of two may be explained by the velocity of transport processes described by the microconstants (Table 3), which were slower than changes in inspiratory concentrations.

Despite the different physicochemical properties of the inhaled anaesthetics, the simulated effects of the confounding factors were similar for isoflurane, desflurane and sevoflurane. Therefore, it appears that comparisons between the pharmacokinetics of these substances based on the method described are valid even if the true errors are at the upper limit of those described above.

Our procedure provides an alternative set of pharmacokinetic parameters that can describe the behaviour of volatile anaesthetics under clinical conditions. Because of the simplicity of the methods used, it appears possible to conduct online estimations of individual pharmacokinetic parameters during anaesthesia. These estimates may serve to predict the individual behaviour of patients, such as forecasting the duration of coasting to a given end-tidal concentration, and thus to improve patient control.

Acknowledgements

We would like to thank Steven L Shafer and Thomas Boullion (both of the Anesthesiology Service, Stanford University School of Medicine, California, USA) for their valuable comments

References

1 Carpenter RL, Eger EI 2nd, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans. *Anesth Analg* 1986; **65**: 575–82

2 Yasuda N, Lockhart SH, Eger EI 2nd, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A. Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology* 1991; **74**: 489–98

3 Yasuda N, Lockhart SH, Eger EI 2nd, Weiskopf RB, Liu J, Laster M, Taheri S, Peterson NA. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991; **72**: 489–98

4 Wissing H, Kuhn I, Rietbrock S, Fuhr U. Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane. *Br J Anaesth* 2000; **84**: 443–9

5 Schwilden H, Tonner PH, Röpcke H. Voraussagbarkeit in- und endexspiratorischer Isofluran- und Enflurankonzentrationen durch pharmakokinetische Modelle und interindividuelle Variabilitat. *Anasthes Intensivther Notfallmed* 1990; **25**, 317–21

6 Lerou JGC, Dirksen R, Beneken Kolmer HH, Booij LHDJ. A system model for closed-circuit inhalation anesthesia. I. Computer study. *Anesthesiology* 1991; **75**: 345–55

7 Lerou JGC, Dirksen R, Beneken Kolmer HH, Booij LHDJ, Borm GF. A system model for closed-circuit inhalation anesthesia. II. Clinical validation. *Anesthesiology* 1991; **75**: 230–7

8 Eger EI 2nd, Guadagni NP. Halothane uptake in man at constant alveolar concentration. *Anesthesiology* 1963; **24**: 299–304

9 Wissing H, Kuhn I. Beeinflussung der inspiratorischen Atemgasmessung durch die Kreisteilkonstruktion und die Beatmungsschlauche. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1997; **32**: S185 [abstract]

10 Press WH, Teukolsky SA, Vetterling WT, Flannery BP. *Numerical recipes in C.* Cambridge: Cambridge University Press, 1992

11 Lin CY. Uptake of anaesthetic gases and vapours. *Anaesth Intensive Care* 1994; **22**: 363–73

12 Epstein RM, Rackow H, Salanitre E, Wolf GL. Influence of the concentration effect on the uptake of anesthetic mixtures: the second gas effect. *Anesthesiology* 1964; **25**: 364–71

13 Korman B, Mapleson WW. Concentration and second gas effect: can the accepted explanation be improved? *Br J Anaesth* 1997; **78**: 618–25

14 Severinghaus JW. The rate of nitrous oxide uptake in man. *J Clinical Invest* 1954; **33**: 1183–9

15 Seber GAF, Wild CJ. *Nonlinear Regression.* New York: Wiley, 1989; 32

British Journal of Anaesthesia **84** (4): 443–9 (2000)

Pharmacokinetics of inhaled anaesthetics in a clinical setting: comparison of desflurane, isoflurane and sevoflurane†

H. Wissing[1]*, I. Kuhn[1], S. Rietbrock[2] and U. Fuhr[2]

[1]Department of Anaesthesiology, Johann Wolfgang Goethe University Hospital, Theodor-Stern-Kai 7, D-60950 Frankfurt am Main, Germany. [2]Institute for Pharmacology, Clinical Pharmacology, Universität zu Köln, Gleuler Strasse 24, D-50931 Köln, Germany

**Corresponding author*

The pharmacokinetic characteristics of desflurane, isoflurane and sevoflurane (16 patients for each anaesthetic) were estimated from measurements of inspired and end-expired agent concentrations and ventilation, obtained during routine anaesthesia in patients undergoing maxillofacial surgery (mean age 38 yr, duration of anaesthesia approximately 2 h). A two-compartment model described the data adequately. Although isoflurane and sevoflurane have almost the same tissue/blood partition coefficients, significant differences between substances were observed for the peripheral volume of distribution (medians and ranges: desflurane, 612 (343–1850) $ml_{vapour}\ kg_{bw}^{-1}$; isoflurane, 4112 (1472–9396) $ml_{vapour}\ kg_{bw}^{-1}$; sevoflurane, 1634 (762–8843) $ml_{vapour}\ kg_{bw}^{-1}$) and the transport clearance from the central to the peripheral compartment (desflurane, 7.0 (4.4–11.1) $ml_{vapour}\ kg_{bw}^{-1}\ min^{-1}$; isoflurane, 30.7 (15.9–38.7) $ml_{vapour}\ kg_{bw}^{-1}\ min^{-1}$; sevoflurane, 13.0 (9.8–22.4) $ml_{vapour}\ kg_{bw}^{-1}\ min^{-1}$). Thus, during clinical anaesthesia the important characteristics of the compounds could be obtained and compared between substances from simple data.

Br J Anaesth 2000; **84**: 443–9

Keywords: anaesthetics volatile, isoflurane; anaesthetics volatile, sevoflurane; anaesthetics volatile, desflurane; pharmacokinetics, models

Accepted for publication: October 12, 1999

The ability to adjust inhalational anaesthesia is determined by the pharmacokinetic features of the anaesthetic agent, such as volumes of distribution and time constants. These variables depend on the physicochemical properties of the compounds and on cardiac output and the distribution of blood flow. Published pharmacokinetic data for inhalation agents have been obtained under controlled experimental conditions in healthy volunteers.[1–4]

To reduce individual variation in pharmacokinetic behaviour and allow comparisons between substances, Carpenter and colleagues[4 5] gave a mixture of potent inhalational anaesthetics (methoxyflurane, halothane, enflurane, isoflurane; totalling 1.1 MAC) in addition to an intravenous anaesthetic. Thus, the pharmacokinetic behaviour of these four compounds, each by itself in subanaesthetic concentration, was measured simultaneously. The number of subjects needed in this design of study is small, and the design has gained wide acceptance. With this method, desflurane was compared with halothane and isoflurane[6] in eight healthy volunteers, and sevoflurane with isoflurane in seven.[7]

In contrast to this procedure, inhalational anaesthesia in patients is carried out with a single volatile anaesthetic. Different inhalational anaesthetics, however, have different effects, such as changes in cardiac output and regional blood flow.[8 9] These concentration-dependent effects[10 11] may influence the uptake and distribution of the agent. Such effects were suggested in the first published volunteer study of the wash-in pharmacokinetics of desflurane.[1] Simultaneous administration of several volatile anaesthetics prevents measurement of the specific effects of each agent,[5 12] and extrapolation from such studies to clinical anaesthesia is questionable.

Additional differences between experimental and clinical anaesthesia are that in clinical practice the inhalational anaesthetic is washed into the patient's breathing system gradually, its concentration has to be adjusted to the stimulus during surgery, and the concentrations used are greater than those used experimentally.

We set out to estimate and compare the pharmacokinetic parameters of the inhalational agents desflurane, isoflurane and sevoflurane during clinical anaesthesia, using a novel method.[13]

---

†This article is accompanied by Editorial I.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Methods

We used data from low-flow anaesthesia from 48 patients undergoing maxillofacial surgery. Patients were matched with respect to ASA classification, age, body weight and procedures with small blood loss. Anaesthesia was with desflurane, isoflurane or sevoflurane (16 patients for each anaesthetic) in a nitrous oxide/oxygen mixture (N_2O >50 vol%/O_2 >30 vol%). After a standard induction with pancuronium bromide 1 mg, sufentanil 0.015–0.02 mg, thiopental 300–500 mg and succinylcholine 60–100 mg, the patient's trachea was intubated. Controlled ventilation was then established and the volatile anaesthetic was given with nitrous oxide. Tidal volume (V_T) was set to 8 ml per kg body weight (bw), and normocapnia or mild hypocapnia was achieved by adjusting the respiratory rate (*RR*), usually between 10 and 12 breaths min^{-1}. Alveolar tidal volume ($V_{T,alv}$) was calculated as the measured tidal volume (V_T) corrected for dead space.[13 14]

The initial fresh gas flow (FGF) was set to 2 litres min^{-1} and was reduced to approximately 1 litre min^{-1} within the first 10 min. The initial vaporiser setting was 2–2.5 vol% for isoflurane and sevoflurane and 8–12 vol% for desflurane. After approximately 10 min, an end-tidal concentration of 1.3 MAC for the respective inhalational anaesthetic in nitrous oxide was achieved. During the subsequent course of anaesthesia, fresh gas flow was further reduced and the concentrations of the volatile anaesthetic were adjusted to the requirements of the surgery. (Sevoflurane is approved by German authorities for use without fresh gas flow restrictions.) Towards the end of surgery, the fresh gas concentration was usually reduced in a coasting phase, and subsequently the volatile anaesthetic and nitrous oxide were washed out with a high fresh gas flow of pure oxygen.

Uptake was calculated as the difference between F_I and F_E' times alveolar ventilation ($V_{T,alv} \bullet RR$). The dose administered was calculated as the area under the uptake curve during the initiation and maintenance of anaesthesia; the dose eliminated at extubation was calculated as the negative area under the uptake curve during the washout period. From these data the dose fraction remaining in the body at extubation was calculated.

The individual concentration–time curves and the uptake were fitted to a two-compartment model as described.[13] The target variables were the volume of distribution for the central compartment (V_1), the transport clearance from the central to the peripheral compartment (Cl_{12}) and the microconstant for distribution from peripheral to central compartment (k_{21}). Based on end-expired concentrations and on the uptake, the parameters were adjusted in an additive variance model so that the calculated end-tidal concentration would correspond as closely as possible to the measured concentration (least-squares method).[13] From these estimates of the target pharmacokinetic parameters, the microconstant for distribution from central to peripheral ($k_{12} = Cl_{12} \bullet V_1^{-1}$), the volume of distribution of the peripheral compartment ($V_2 = Cl_{12} \bullet k_{21}^{-1}$) and the steady-state volume ($V_{ss} = V_1 + V_2$) were calculated.

Table 1 Characteristics of the patients and duration of anaesthesia in the three groups. Age is median (range), all other values are mean (SD). There were no statistically significant differences between the three groups

	Desflurane	**Isoflurane**	**Sevoflurane**
Number of participants (males:females)	16 (12:4)	16 (15:1)	16 (12:4)
Age (yr)	33 (29–69)	32 (21–73)	36 (21–61)
Body weight (kg)	73 (10)	70 (8)	70 (11)
Body height (cm)	175 (7)	176 (8)	173 (10)
BMI (kg m^{-1})	23.7 (2.1)	22.3 (2.9)	23.7 (2.1)
Duration of anaesthesia (min)	111 (44)	148 (41)	115 (57)

The variables were characterized by their medians and ranges. To check whether baseline characteristics between treatment groups were similar, a comparison of physical characteristics of the patients and of the duration of anaesthesia was carried out using multiple analysis of variance (MANOVA). An exploratory comparison of the pharmacokinetic variables for desflurane, isoflurane and sevoflurane was calculated using the Mann–Whitney *U* test and 95% confidence intervals based on the Hodges–Lehmann estimator[15] (BIAS software).[16] Using the logarithmically transformed values of the parameters the Hodges–Lehmann estimator comparies two random samples by calculating the median ratio of all combinations. If the resulting 95% confidence interval includes unity, then no statistical difference between the samples exists. If 1.0 is encountered outside this interval, a difference is confirmed applying a significance level of $P<0.05$.

Additionally, analysis of covariance (ANCOVA) was used to check whether gender (nominal covariate), age, body mass index and/or the duration of anaesthesia (continuous covariates) had an influence on the target pharmacokinetic variables V_1, Cl_{12} and k_{21} in the whole data set ($n = 48$). As the inhalational anaesthetics were expected to differ in pharmacokinetic properties, the agent was included in the model as a nominal covariate. Assuming a factorial model, logarithmically transformed values for pharmacokinetic parameters were used in the ANCOVA. Interactions between covariates supposed to affect pharmacokinetics were not taken into account, since a sample of 48 was not large enough to reliably test 10 two-fold and a number of higher interactions between covariates in addition to their main effect. The main question was whether the covariates had an effect on the pharmacokinetic parameters, and there was no *a priori* evidence that interactions between covariates are important. The calculations were carried out using SPSS 7.5, module General Multivariate (SPSS Inc., Chicago, IL, USA).

Results

Table 1 gives the characteristics of the patients and the duration of anaesthesia in the patients. There were no statistically significant differences between the groups

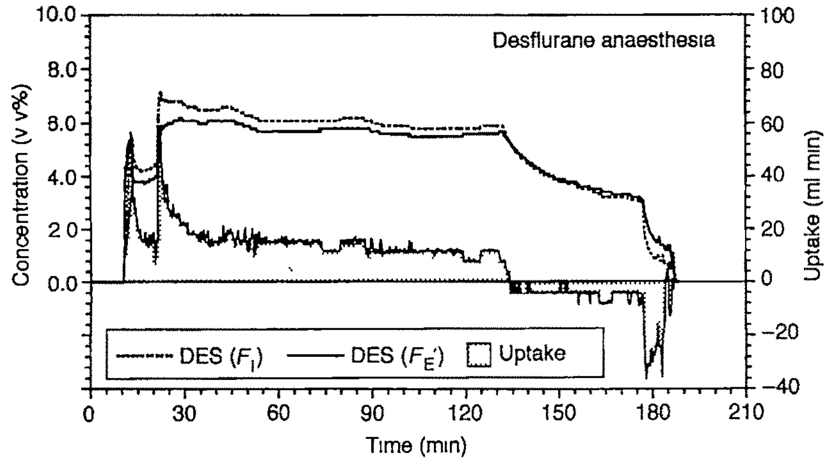


Fig 1 Concentration–time plots (F_I, F_E') and uptake during 3 h of inhalation anaesthesia with desflurane in a representative individual. The uptake (shaded area) depends on the difference F_I–F_E' and alveolar ventilation. Uptake during absorption ($F_I>F_E'$) corresponds to the dose administered and uptake during elimination ($F_I<F_E'$) to the dose eliminated. Initially, there were two rapid concentration changes. The second was carried out at 1 litre min^{-1} fresh gas flow (FGF), setting the vaporiser to 18. In steady-state uptake, absorption was in the same range as that during anaesthesia with isoflurane in Figure 2, but showed a slight decrease with time. In comparison with the isoflurane and sevoflurane anaesthesia shown in Figures 2 and 3 respectively, the long coasting period (vaporiser set to 0) (between 130 and 175 min) and the larger negative component of the uptake curve are noteworthy. Elimination occurred even during coasting The wash-out period at 3 L FGF until extubation took 12 min.

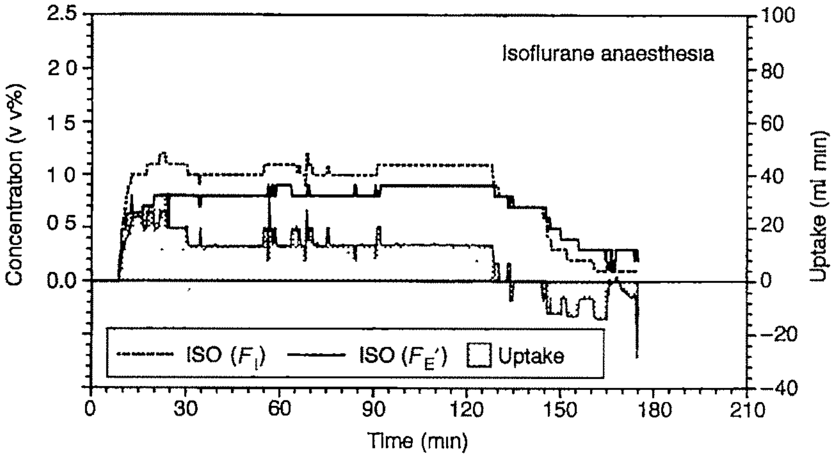


Fig 2 Concentration–time plots (F_I, F_E') and uptake measured at the tube-connector during approximately 3 h of inhalation anaesthesia with isoflurane in a representative individual. The uptake (shaded area) during absorption ($F_I>F_E'$) corresponds to the dose administered and uptake during elimination to the dose eliminated via the lungs. After the initial 30 min, the uptake remained largely constant. The coasting phase under minimal flow conditions (130–145 min) was markedly shorter than in Figure 1, and during coasting F_I was still greater or equal to F_E', indicating that distribution from the central into the peripheral compartment caused a faster F_E' decrease than anaesthetic elimination from the circle under minimal flow conditions. The wash-out phase at 3 L FGF until extubation was >30 min, and was longer than for desflurane and sevoflurane anaesthesia in Figures 1 and 3 respectively.

(MANOVA), but the mean duration of anaesthesia in patients receiving isoflurane was approximately 30% longer than that for the other anaesthetics.

Figures 1, 2 and 3 represent typical examples of time courses for the inspiratory and end-tidal concentrations and the resulting uptake or elimination during anaesthesia with desflurane (Fig. 1), isoflurane (Fig. 2) and sevoflurane (Fig. 3). Saturation occurred most rapidly with desflurane, shown by the small difference between F_I and F_E'. The greater elimination of the compound is shown by the greater proportion of the negative area between the uptake curve and the abscissa. Sevoflurane had an intermediate position between desflurane and isoflurane. The gradient between F_I and F_E' declined faster for sevoflurane than for isoflurane but most rapidly with desflurane. The absolute uptake was smallest with sevoflurane, but in proportion to F_E' this was about twice as great as the uptake of desflurane.

Table 2 shows the values for the administered, eliminated and residual doses as calculated from the uptake. Although the inspired concentration was much greater for desflurane than for isoflurane, the median of the administered dose was only 50% greater. Compared with the administered dose, the median quantity exhaled via the lungs by the time of extubation was 24% for desflurane and about 10% for isoflurane and sevoflurane.

The pharmacokinetic features of the three compounds

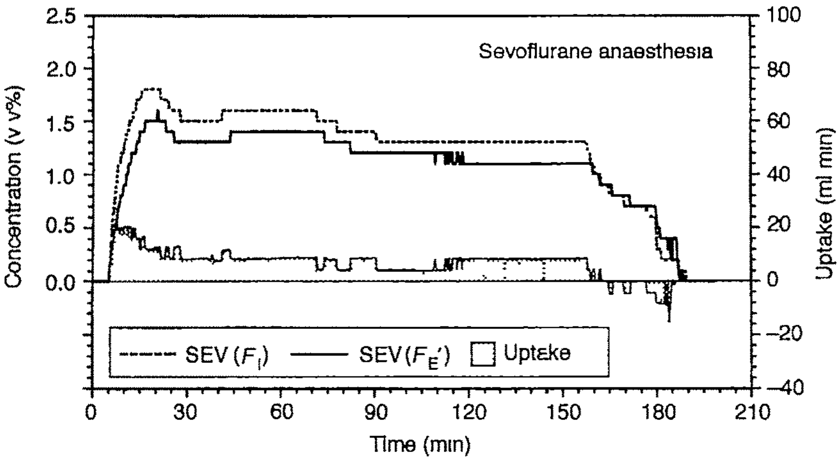


Fig 3 Concentration–time curves (F_I, F_E') and uptake measured at the tube-connector during 3 h of inhalation anaesthesia with sevoflurane in a representative individual. The uptake (shaded area) during absorption (F_I>F_E') corresponds to the dose administered, and the uptake during elimination (F_I<F_E') to the dose eliminated via the lungs. Absolute uptake during steady state was lowest with sevoflurane, but in relation to the end-tidal concentration it was twice as high as that of desflurane. Coasting was shorter than with desflurane (Fig. 1) while uptake was zero, indicating that distribution into the peripheral compartment was as fast as anaesthetic elimination from the circle under minimal flow conditions. The duration of the wash-out phase at 3 L FGF until extubation was similar to that with desflurane anaesthesia in Figure 1

Table 2 Medians and ranges of the directly calculated parameters *The dose remaining in the body at extubation for desflurane was significantly different (P<0 05) from that for isoflurane and sevoflurane, which did not differ from each other

	Desflurane	Isoflurane	Sevoflurane
Dose administered (ml_{vapour})	1757 (717–3086)	1143 (82–1189)	649 (282–1786)
Dose eliminated (ml_{vapour})	367 (174–819)	102 (36–593)	62 (25–286)
Dose not yet eliminated at extubation (% of dose administered)	76 (55–88)	90* (81–95)	91* (80–97)

could be described adequately in all patients using a two-compartment model,[13] which is therefore used in all further consideration of the compounds. Since only 50% of the profiles permitted an adequate fit to a three-compartment model, the latter was discarded for this evaluation. The estimates of pharmacokinetic parameters are shown in Table 3. For comparison between the compounds, Table 4 gives the ratios of the respective parameters between the agents and 95% confidence intervals calculated using the Hodges–Lehmann estimator. Significant differences are marked with an asterisk.

The microconstants k_{12}, describing distribution from the central (1) into the peripheral (2) compartment, and k_{21}, describing the redistribution and the corresponding transport clearance (Cl_{12}), show that isoflurane and sevoflurane are distributed into the peripheral compartment faster than desflurane. For desflurane the equilibrium constant k_{12}/k_{21} showed a more pronounced balance towards redistribution than for the other compounds. The ratios differed from those of k_{12}, as the equilibrium constant is influenced by k_{21}. The microconstants obtained for sevoflurane and isoflurane did not differ.

Using ANCOVA, the covariates tested explained jointly 77%, 87% and 50% of the overall variability for V_1, Cl_{12}, and k_{21} respectively. Whereas the only significant influence on k_{21} was exerted by duration of anaesthesia, Cl_{12} and, to a lesser extent, V_1 depended primarily on the volatile anaesthetic agent used (Table 5). Duration of anaesthesia as well as patient age had also a significant effect on V_1.

Comparisons between compounds for pharmacokinetic parameters depending largely upon tissue/blood partition coefficients, i.e. V_2 and Cl_{12}, are shown together with ratios for published partition coefficients[17] in Table 6. The marked difference in pharmacokinetic characteristics of the compounds exceeded those in the respective tissue/blood partition coefficients.

Discussion

The determination of the pharmacokinetic profiles of inhalational anaesthetics using respiratory gas analysis is an established method.[4–7 18] The analytical procedures for volatile anaesthetics described in the literature depend primarily on gas chromatography assays, which permit the determination of concentrations over several orders of magnitude. This high sensitivity is required particularly for the determination of minute concentrations several days after exposure.

In this study, we used those data which are now routinely available from anaesthetic workstations. As described in the accompanying paper,[13] the data gathered during routine monitoring, i.e. F_I, F_E' and ventilatory parameters, are sufficient to provide reliable estimates of the pharmacokinetic parameters. This allowed the compounds to be characterised under clinical conditions. Although the estimates were derived from and therefore are valid for the duration of anaesthesia, it remains to be investigated to what extent they also apply to the time after extubation, and how long anaesthesia must be maintained until the

Table 3 Absolute values for the estimated pharmacokinetic variables and extrapolated parameters. Values are median (range). k_{12} = microconstant for transport from central to peripheral compartment, k_{21} = microconstant peripheral to central compartment; Cl_{12} = transport clearance from central to peripheral compartment, V_1 = volume of distribution of the central compartment, V_2 = volume of distribution of the peripheral compartment, V_{ss} = total volume of distribution during steady state V_1, V_2 and V_{ss} are given as millilitres of inhaled anaesthetic in relation to body weight. Group differences are given in Table 4 as the ratios for the parameters

	Desflurane	**Isoflurane**	**Sevoflurane**
k_{12} (min^{-1})	0.078 (0.029–0.186)	0.158 (0.065–0.583)	0.117 (0.070–0.344)
k_{21} (min^{-1})	0.011 (0.003–0.022)	0.007 (0.001–0.014)	0.007 (0.001–0.019)
k_{12}/k_{21}	9.3 (4.6–27.5)	23.2 (10.8–40.8)	18.5 (8.5–57.5)
Cl_{12} (ml_{vapour} kg^{-1} min^{-1})	7.0 (4.4–11.1)	30.7 (15.9–38.7)	13.0 (9.8–22.4)
V_1 (ml_{vapour} $kg_{bw}{}^{-1}$)	75 (49–140)	196 (37–332)	106 (57–171)
V_2 (ml_{vapour} $kg_{bw}{}^{-1}$)	612 (343–1850)	4112 (1472–9396)	1634 (762–8843)
V_{ss} (ml_{vapour} $kg_{bw}{}^{-1}$)	698 (408–1917)	4285 (1509–9640)	1748 (819–8997)

Table 4 Comparison of the pharmacokinetic parameters between anaesthetics The ratios isoflurane/desflurane, sevoflurane/desflurane, isoflurane/sevoflurane and their 95% confidence intervals (CI) were calculated using the Hodges–Lehmann estimator. *Significant group differences at $P<0.05$. For explanation of pharmacokinetic parameters, see legend to Table 3

	Isoflurane/ desflurane	**Sevoflurane/ desflurane**	**Sevoflurane/ isoflurane**
k_{12}	1.81* (1.32–2.57)	1.52* (1.12–2.36)	0.82 (0.58–1.29)
k_{21}	0.71 (0.44–1.17)	0.67 (0.41–1.22)	0.96 (0.59–1.56)
k_{12}/k_{21}	2.72* (1.78–3.77)	2.40* (1.54–3.71)	0.90 (0.60–1.36)
Cl_{12}	4.21* (3.40–5.26)	2.03* (1.59–2.55)	0.47* (0.39–0.58)
V_1	2.45* (1.80–3.19)	1.28 (0.97–1.66)	0.52* (0.39–0.73)
V_2	6.09* (4.01–9.09)	2.89* (2.02–4.71)	0.48* (0.30–0.79)
V_{ss}	5.58* (3.78–8.26)	2.70* (1.95–4.25)	0.48* (0.31–0.8)

Table 5 Results of ANCOVA for the effect of independent variables on pharmacokinetic parameters Estimates obtained for logarithmic pharmacokinetic parameters were transformed to factors describing the difference in pharmacokinetics attributable to those variables For instance, desflurane had a 0.551-fold lower V_1 than isoflurane, and V_1 increased 1.181-fold with every hour of duration of anaesthesia *Significant ($P<0.05$) contribution of the influencing variable to overall variation For abbreviations, see legend to Table 3

Influencing variable	**Mean resulting difference (factor)**		
	V_1	Cl_{12}	k_{21}
Inhalational anaesthetic			
Desflurane/isoflurane	0.551*	0.212*	0.993
Sevoflurane/ isoflurane	0.704*	0.458*	0.720
Gender			
Female/male	0.927	1.215	1.020
Age (per year)	0.986*	0.998	0.986
BMI (per kg m^{-2})	0.967	0.994	0.955
Duration of anaesthesia (per h)	1.181*	0.934	0.632*

Table 6 To relate estimated pharmacokinetic parameters to physicochemical characteristics, the ratios between substances for the tissue/gas and tissue/blood equilibrium partition coefficients were calculated from published data [17] Values for V_2 and Cl_{12} obtained in this study, depending largely upon tissue/blood partition coefficients, are included to facilitate comparison. All estimated ratios for pharmacokinetic parameters (see also Table 4) differ from those expected from the differences in physicochemical properties For pharmacokinetic parameters, see legend to Table 3

Partition coefficient ratio[17]	**Isoflurane/ desflurane**	**Sevoflurane/ desflurane**	**Sevoflurane/ isoflurane**
Blood/gas	3.16	1.62	0.51
Brain/blood	1.21	1.31	1.08
Heart/blood	1.25	1.34	1.1
Liver/blood	1.33	1.41	1.06
Kidney/blood	1.11	1.22	1.1
Muscle/blood	1.44	1.54	1.07
Fat/blood	1.65	1.75	1.06
V_2 (this study)	6.09	2.89	0.48
Cl_{12} (this study)	4.21	2.03	0.47

information gathered will allow reliable prediction of concentrations in the further course of anaesthesia.

Apparent volumes of distribution were clearly smaller for desflurane than for sevoflurane and isoflurane (Tables 3 and 4). This was most pronounced for the peripheral volume. Distribution from the central to the peripheral compartment was much more rapid for isoflurane than for sevoflurane and was slowest for desflurane, whereas the redistribution (k_{21}) was only slightly greater for desflurane and sevoflurane than for isoflurane, and not significantly so. This minor difference may be explained by a 30% longer mean duration of isoflurane anaesthesia (Table 1). Duration of anaesthesia significantly decreased the apparent k_{21} and, to a lesser extent, increased the apparent V_1 in the ANCOVA (Table 5). It may be that k_{21} reflects the effect of a third compartment which has increasing relevance as the duration of anaesthesia increases. Minor differences in baseline characteristics between treatment groups, however, are not expected to invalidate comparisons, because the pharmacokinetic differences between agents estimated by ANCOVA as a parametric approach (Table 5) gave results very similar to the Hodges–Lehmann estimator (Table 4). The equilibrium constant (k_{12}/k_{21}) was about 2.5 times smaller for desflurane than for sevoflurane and isoflurane (Tables 3 and 4), confirming the less extensive distribution of desflurane. This could be a disadvantage for isoflurane with respect to the control of the anaesthesia, because pronounced distribution into peripheral compartments causes a continuous large uptake and thus slower saturation of the central compartment. In contrast, the slower distribution of desflurane (small Cl_{12}) supports the more rapid saturation of the central compartment. The specific distribution behaviour thus turns out to be a relevant parameter besides the concentration of agent, cardiac output and physicochemical properties, including solubility in blood, which determine the wash-in behaviour and the intraoperative control of an inhalational anaesthetic. Cl_{12} of sevoflurane is two times that of desflurane. Its uptake with respect to the end-tidal concentration was about twice as high than that of desflurane. High uptake and high clearance into the periphery become important in the control of 'Low and Minimal Flow' anaesthesia, in which, compared with high-flow applications, the capacity for agent delivery is close to the uptake by the patient (determined by the concentration range of the vaporiser and fresh gas flow: 1 litre min^{-1} in low-flow and 0.5 litre min^{-1} in minimal-flow applications). Because of limited agent delivery in these circumstances, rapid distribution to the periphery considerably reduces the velocity of the concentration changes in the central compartment and makes it difficult to increase the depth of anaesthesia by increasing anaesthetic concentrations. In recovery, our data indicate that, during the wash-out period until extubation, pulmonary elimination of isoflurane and sevoflurane is less than that of desflurane (Table 2).

The observation time between intubation and extubation was insufficient to give a valid fit to a model with more than two compartments in 50% of the cases. In none of the patients could more than three compartments be fitted reliably.[4] However, a fourth and even a fifth compartment have been described in other studies[5–7] with measurements for 5–9 days after experimental anaesthesia. Over this time-span, ventilation has been assumed to correspond to that seen in normal activity of the persons under investigation. How complex a model is needed to 'correctly' describe the pharmacokinetics of an inhalational anaesthetic and how realistic are the underlying assumptions?[19 20] This depends on the context of the question which is to be addressed by means of the model. Hypotheses about the proportion of a compound remaining in the body and possible subsequent metabolism may require complex multicompartment models. A precise allocation of several hypothetical peripheral compartments to anatomical defined tissues, however, is hardly feasible. In contrast, to describe the pharmacokinetics of inhaled anaesthetics during clinical anaesthesia in order to compare agents in clinical practice or to improve patient control, our simplified model appears sufficient.[13]

The tables show marked variation in the pharmacokinetic parameters. To reduce this variation, the concept of simultaneous administration of potent inhalation anaesthetics was developed.[4 5] Using this method, the haemodynamic conditions and regional blood flow are identical for all compounds.[5] Any specific effects of the substances on these factors, which may in certain cases affect the kinetics and clinical features quite considerably, remain undetected by this method.[12] The possibility that two simultaneously administered inhalation anaesthetics could mutually influence their solubility appears negligible,[21] yet interactions with the metabolism of other substances and their plasma protein binding have been described *in vitro*,[22–24] and specific plasma protein binding has been described at least for halothane.[25] Metabolic interactions between inhalational anaesthetics were demonstrated in animals after sequential administration,[26 27] but could not be confirmed in man during simultaneous administration.[28] Even so, substance-specific effects of the higher clinical doses on the micro- and macrocirculation suggest that pharmacokinetic data from this type of volunteer experiment may differ from those obtained clinically.

Comparison of the volumes of distribution from our data with those from Yasuda and colleagues,[6 7] derived from the simultaneous application of inhaled anaesthetics, is possible only to a limited extent as the models applied in the studies are different. Yasuda and colleagues[6 7] found for halothane, isoflurane, desflurane and sevoflurane almost equal tissue blood flows and tissue volumes, indicating that the size of the virtual volumes of distribution varies according to the partition coefficients. This pattern of distribution relates to a time point when all redistribution processes were in steady state or when the compounds under investigation were distributed and redistributed under almost identical conditions.

For the time between intubation and extubation, our data suggest that the observed differences between the volumes of distribution are not fully explained by differences in the partition coefficients of the compounds (Table 6). The peripheral volume of distribution for isoflurane is more than 6 times and that of sevoflurane more than 2 times greater than that of desflurane (Table 4). There is no tissue for which a difference in partition coefficient of that magnitude has been described. Therefore, differences in blood flow distribution must be considered. For isoflurane, it appears that during anaesthesia a pronounced redistribution of blood flow occurs into organs with large storage capacity. For sevoflurane this effect seems to be less pronounced. This assumption is supported by the data for the transport clearance Cl_{12}, the most stable parameter,[13] which is more than 4 times greater for isoflurane and about 2 times greater for sevoflurane than for desflurane, yet it should be only 1.5-fold greater if only the tissue/blood partition coefficients are considered (Table 6). Unexpectedly large peripheral volumes of distribution, which correspond to considerable uptake, have indeed been described for isoflurane during clinical anaesthesia.[4] The finding that isoflurane, even at concentrations around 1 MAC in oxygen, markedly increased the blood flow into muscle tissue in humans[29] and in animal experiments might serve as an explanation.[10] Thus, the pharmacokinetic parameters of our simple two-compartment model could provide a better description of intraoperative processes than the differences in tissue solubility[30] between desflurane and isoflurane.

Because of a slower distribution into a smaller V_2 for desflurane compared with isoflurane or sevoflurane, distribution processes should contribute only slightly to the decrease in concentration in the central compartment after 2 h of anaesthesia with desflurane. However, recent reports on anaesthetic uptake at constant end-tidal concentrations in closed systems describe, after an initial wash-in, a constant rather than a declining uptake of desflurane and isoflurane[31 32] in the first hour of anaesthesia. These results are said to be in contrast[32] to the square root of time model of anaesthetic uptake of Lowe and Ernst[33] and the predictions derived from multicompartment models.[6,34] The two-compartment model, however, was reliably fitted to the measured parameters. Although the model implies decay of uptake, it seems to be almost constant after several minutes (Figs 1 and 2), at constant end-tidal concentrations. With respect to the time constant of distribution, the changes are too small to show a distinct decrease. Thus, uptake appears to be constant, although a biexponential fit for uptake is appropriate.[32]

In conclusion, data from clinical anaesthesia records allow important features of desflurane, isoflurane and sevoflurane to be derived and compared between agents without additional sampling from the patient. The results support clinical observations and data derived from other settings showing that distribution into peripheral compartments is most pronounced for isoflurane and least pronounced for desflurane.

References

1 Jones RM, Cashman JN, Eger EI 2nd, Damask MC, Johnson BH. Kinetics and potency of desflurane (I-653) in volunteers *Anesth Analg* 1990; **70**: 3–7

2 Cromwell TH, Eger EI 2nd, Stevens WC, Dolan WM. Forane uptake, excretion, and blood solubility in man. *Anesthesiology* 1971; **35**: 401–8

3 Mapelson WW. The rate of uptake of halothane vapour in man. *Br J Anaesth* 1962; **34**: 11–18

4 Carpenter RL, Eger EI 2nd, Johnson BH, Unadkat JD. A new concept in inhaled anesthetic pharmacokinetics. *Anesth Analg* 1984; **64**: 197

5 Carpenter RL, Eger EI 2nd, Johnson BH, Unadkat JD, Sheiner LB Pharmacokinetics of inhaled anesthetics in humans. *Anesth Analg* 1984; **65**: 575–82

6 Yasuda N, Lockhart SH, Eger EI 2nd, Weiskopf RB, Johnson BH, Freire BA, Fassoulaki A. Kinetics of desflurane, isoflurane, and halothane in humans. *Anesthesiology* 1991; **74**: 489–98

7 Yasuda N, Lockhart SH, Eger EI 2nd, Weiskopf RB, Lui J, Laster M, Taheri S, Peterson NA. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991; **72**: 316–24

8 Conzen P, Peter K. Inhalationsanasthetika: Pharmakodynamik. In: Doenike A, Kettler D, List WF, Tarnow J, eds. *Lehrbuch der Anasthesiologie und Intensivmedizin· Anasthesiologie.* Berlin: Springer, 1992; 133

9 Palvin EG, Su JY. Cardiopulmonary pharmacology. In: Miller RD, ed. *Anesthesia.* New York: Churchill Livingstone, 1994; 125

10 Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. *Anesth Analg* 1984; **63**: 557–65

11 Hartmann JC, Pagel PS, Proctor LT, Kampine JP, Schmeling WT. Influence of desflurane, isoflurane and halothane on regional perfusion in dogs. *Can J Anaesth* 1992; **39**. 877–87

12 Zbinden A, Thomson D. Inhalationsanasthetika: Pharmakokinetik. In· Doenike A, Kettler D, List WF, Tarnow J, eds. *Lehrbuch der Anasthesiologie und Intensivmedizin. Anasthesiologie.* Berlin: Springer, 1992: 118

13 Rietbrock S, Wissing H, Kuhn I, Fuhr U. Pharmacokinetics of inhaled anaesthetics in a clinical setting: evaluation of a method based on routine monitoring data. *Br J Anaesth* 2000; **84**: 437–42

14 Eger EI 2nd, Guadagni NP. Halothane uptake in man at constant alveolar concentration. *Anesthesiology* 1963; **24**: 299–04

15 Hollander M, Wolfe DA. *Nonparametric Statistical Methods* New York: Wiley, 1973; 75–8

16 Ackermann H. *WinBIAS. Biometrische Analyse von Stichproben,* Version 7.01. Hochheim-Darmstadt, Gemany. Epsilon-Verlag, 1998

17 Eger EI 2nd, Bahlman SH. Is the endtidal anesthetic partial pressure an accurate measure of the arterial anesthetic partial pressure? *Anesthesiology* 1971; **35**: 301–3

18 Yasuda N, Targ AG, Eger EI 2nd. Solubility of I-653, sevoflurane, isoflurane, and halothane in human tissues. *Anesth Analg* 1989, **69**. 370–3

19 Beneken Kolmer HH, Burm AG, Cramers CA, Ramakers JM, Vader HL The uptake and elimination of halothane in dogs· a two or multi compartment system? II: Evaluation of wash-in and wash-out curves. *Br J Anaesth* 1975; **47**. 1169–75

20 Mapleson WW. Pharmacokinetic models· simple or complex? (Letter) *Br J Anaesth* 1977; **49**· 88

21 Coburn CM, Eger EI 2nd. The partial pressure of isoflurane and halothane does not affect their solubility in rabbit blood or brain or human brain: inhaled anesthetics obey Henry's Law. *Anesth Analg* 1986; **65**. 960–2

22 Dale O, Nilsen OG. Displacement of some basic drugs from human serum proteins by enflurane, halothane and their major metabolites. An in vitro study *Br J Anaesth* 1984; **56**. 557–61

23 Dale O, Gandolfi AJ, Brendel K, Schuman S Rat liver slices and diazepam metabolism. in vitro interactions with volatile anaesthetic drugs and albumin. *Br J Anaesth* 1988; **60**: 692–6

24 Dale O, Frink EJ, Thommesen L, Gandolfi AJ. Hepatic elimination of diazepam: interactions with albumin, desflurane and sevoflurane. *Br J Anaesth* 1994; **70**: 454–5

25 Johansson JS, Eckenhoff RG, Dutton L Binding of halothane to serum albumin demonstrated using tryptophan fluorescence. *Anesthesiology* 1995; **83**· 316–24

26 Fisgerova-Bergerova V. Inhibitory effect of isoflurane upon oxidative metabolism of halothane. *Anesth Analg* 1984; **63**: 399–04

27 Fish JK, Rice SA. Halothane inhibits metabolism of enflurane in Fisher 344 rats. *Anesthesiology* 1983, **59**: 417–20

28 Carpenter RL, Eger EI 2nd, Johnson BH, Unadkat JD, Sheiner LB The extent of metabolism of inhaled anesthetics in humans. *Anesthesiology* 1986; **65**: 201–5

29 Stevens WC, Cromwell TH, Halsey MJ, Eger EI 2nd, Shakespeare TF, Bahlman SH. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at a constant arterial carbon dioxide tension. *Anesthesiology* 1971; **35**: 8–16

30 Hargasser S, Hipp R, Breibauer B, Mielke L, Entholzner E, Rust M. A lower solubility recommends the use of desflurane more than the isoflurane, halothane, and enflurane under low-flow conditions. *J Clin Anesth* 1995; **7**: 49–53

31 Hendrickx JFA, Soetens M, Van der Donk A, Meeuwis H, Smolders F, De Wolf AM. Uptake of desflurane and isoflurane during closed-circuit anesthesia with spontaneous and controlled ventilation. *Anesth Analg* 1997; **84**: 413–8

32 Walker TJ, Chakrabati MK, Lockwood GG. Uptake of desflurane during anaesthesia. *Anaesthesia* 1996; **51**: 33–6

33 Lowe HJ, Ernst EA. *The Quantitative Practice of Anaesthesia – Use of Closed Circuit.* Baltimore: Williams & Wilkins, 1981

34 Eger EI 2nd. Complexities overlooked. things may not be what they seem. *Anesth Analg* 1997; **84**: 239–40

British Journal of Anaesthesia **84** (4): 450–5 (2000)

General *versus* regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials

S. C. Urwin*, M. J. Parker[2] and R. Griffiths[1]

[1]Anaesthetic Department and [2]Orthopaedic Department, Peterborough District Hospital, Thorpe Road, Peterborough PE3 6DA, UK

**Corresponding author: Anaesthetic Department, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK*

Hip fracture surgery is common and the population at risk is generally elderly. There is no consensus of opinion regarding the safest form of anaesthesia for these patients. We performed a meta-analysis of 15 randomized trials that compare morbidity and mortality associated with general or regional anaesthesia for hip fracture patients. There was a reduced 1-month mortality and incidence of deep vein thrombosis in the regional anaesthesia group. Operations performed under general anaesthesia had a reduction in operation time. No other outcome measures reached a statistically significant difference. There was a tendency towards a lower incidence of myocardial infarction, confusion and postoperative hypoxia in the regional anaesthetic group, and cerebrovascular accident and intra-operative hypotension in the general anaesthetic group. We conclude that there are marginal advantages for regional anaesthesia compared to general anaesthesia for hip fracture patients in terms of early mortality and risk of deep vein thrombosis.

Br J Anaesth 2000; **84**: 450–5

Keywords: anaesthesia, general; anaesthesia, regional; surgery, hip fracture; meta-analysis

Accepted for publication: November 11, 1999

Hip fracture is a common condition and is increasing in incidence. In 1990, there were an estimated 1.7 million hip fractures worldwide. Predictions for numbers presenting in 2050 are as high as 6.3 million globally.[1] Females predominate, at a ratio of 4:1, indicating their increased susceptibility to fractures due to osteoporosis.[2]

Most hip fractures are treated surgically, either by internal fixation of the fracture or by replacement of the femoral head with an arthroplasty. The high incidence of hip fracture confers a considerable load on surgical and anaesthetic services. Furthermore, this group of patients has an average age of approximately 80 yr and intercurrent illnesses such as cardiac and respiratory disease are common. These problems result in hip fracture being associated with significant morbidity and mortality.

Anaesthesia for hip fracture most commonly involves either a general or a regional anaesthetic. General anaesthesia may be induced and maintained by a number of drugs, depending on the anaesthetist's preference and the condition of the patient. The airway may be maintained using a face mask, laryngeal mask or endotracheal tube, and ventilation may be spontaneous or mechanical. Regional anaesthesia usually takes the form of a spinal injection of local anaesthetic to induce surgical anaesthesia, but epidural anaesthesia may also be used. Sedatives are often used in conjunction with regional anaesthesia to help the patient tolerate positioning during placement of the spinal or epidural needle and also during the intra-operative period. Previous studies have failed to establish a benefit of one form of anaesthetic over another.[3 4] A previous meta-analysis of 11 trials[3] showed no difference in outcome with different anaesthetic methods but not all published randomized trials were included. In addition, data from one trial was duplicated in two other trials by the same author. The purpose of this study was to extend and correct the work done previously using a more comprehensive search of the literature in order to determine if there is a difference in outcome depending on the type of anaesthetic used in hip fracture patients.

Methods

Search strategy and study selection

Randomized and quasi-randomized trials were identified using the search strategy of the Musculoskeletal Injuries Review Group of the Cochrane Collaboration.[5] This included searching the computer databases of Medline, Embase, CINAHL, Current contents and the Cochrane controlled trials register. In Medline the search method used was that described by Dickerson.[6] In addition we searched using the references of all identified trials and review articles along with hand-searching of core journals and

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

abstract books of orthopaedic conferences. Articles in all languages were included and translations were obtained for any trials published in foreign languages. Where relevant, further information was sought from trial authors. Trials comparing different anaesthetic techniques for hip fracture repair that reported mortality or any aspect of morbidity were considered for inclusion. Trials were excluded if they compared outcome following different doses of drug for the same anaesthetic technique, and those comparing different general anaesthetic techniques.

Data extraction and quality assessment

Independent reviewers (SCU, RG) assessed methodological quality using a nine item scoring system. The items assessed were:

(i) the method of randomization,
(ii) inclusion and exclusion criteria for patients entered into the study,
(iii) adequate description of treatment and control groups at entry to the study,
(iv) if the care programmes were identical between the groups other than the anaesthetic type,
(v) clear definition of the outcome measures in the text,
(vi) blinding of the assessors to the treatment group,
(vii) adequate patient follow-up (a minimum of 3 months was taken as adequate),
(viii) number of patients lost to follow-up (less than 5% lost to follow-up was taken as acceptable) and
(ix) statistical analysis on an intention-to-treat basis.

Each study could score a maximum of 11 for methodological quality. The method of randomization was considered the most important factor and could score a maximum of three points. All other items could score one point only. Any difference in opinion between the assessors was resolved by discussion with a third reviewer (MJP).

Outcome measures sought in each paper included intra-operative details and data related to post-operative morbidity and mortality. Intra-operative details included length of operation, blood loss, transfusion requirements and the occurrence of hypotension. Morbidities included post-operative hypoxia, pneumonia, thromboembolism, confusion, renal failure, myocardial infarction, congestive cardiac failure, urinary retention and vomiting. Complications relating to the type of anaesthesia, such as dental damage in general anaesthesia and post-dural puncture headache for spinal anaesthesia were sought. Length of hospital stay, long term functional and quality of life outcomes were also sought.

Data analysis

Review Manager software[7] was used to analyse the outcome data. Heterogeneity between comparable trials was tested using a standard chi-square test. Where $P<0.1$ for heterogeneity, a random effects analysis was carried out. Pooled Peto odds ratios (OR) were calculated for dichotomous outcomes, and pooled weighted mean differences for continuous variables. Ninety five per cent confidence intervals were derived in both cases. Full details of the data analysis and methodology are presented elsewhere.[5]

Results

Patients and studies included

Fifteen trials involving a total of 2162 patients with hip fracture were included[8–25] Details of these trials are summarized in Table 1. A full list of the excluded trials considered for review is available elsewhere,[5] as are full data of the individual studies included in this meta-analysis. The majority of excluded studies involved comparisons outside the scope of this review, and one trial was excluded because all patients receiving a regional anaesthetic also had a general anaesthetic.[26] Two excluded trials involved neuroleptanaesthesia which was considered to be no longer appropriate for hip fracture surgery, and were therefore excluded.[27 28] One study was excluded as it recorded injected indocyanine green clearance as its only outcome measure.[29] Attention is drawn to the three trial reports by McKenzie and colleagues.[19–21] All of these involve patients from one trial.[20] This study contains results from the whole trial population, whereas the other two trials involved only subgroups of patients. For the purpose of this review, all three papers are referred to as 'McKenzie 1984', and data from the 1980 and 1985 papers were only included if these were unavailable in the original paper. A spinal anaesthetic was used in all trials except one which used an epidural technique.[14]

Outcome measures

Tables 2 and 3 summarize the comparison of outcome between regional and general anaesthesia for all outcome measures studied.

Mortality was reported in 11 studies, data being available at 1 month or beyond in eight studies.[9 14–16 20 22 23 25] Table 2 shows the significant reduction in mortality at 1 month, but this advantage did not extend to 3 months or beyond.

Most studies reported the length of operation. Pooling of results was possible for six studies,[9–11 18 20 23] indicating a significant reduction in the surgical times for general anaesthesia (weighted mean difference 4.8 min, 95% CI 1.1–8.6 min).

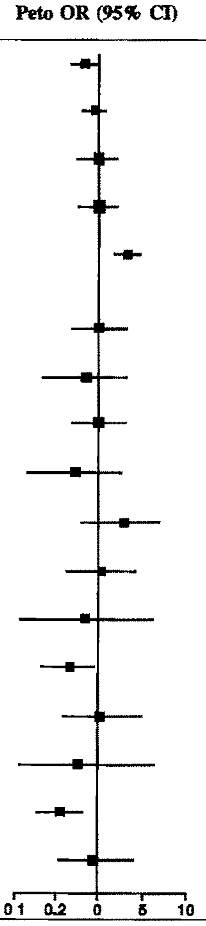
Summation of the reported occurrence of intra-operative hypotension was possible from six studies.[9 14 15 18 22 23] There was significant heterogeneity of these results (chi-square 11.9, $P<0.05$). Using fixed effects analysis, hypotension was significantly less frequent in the general anaesthetic group: 116/447 (26.0%) in the general anaesthetic group compared with 146/426 (34.3%) in the regional anaesthetic group (Peto OR 1.5, 95% CI 1.1–2.0). However, analysis using a random effects model, revealed a non-significant tendency to a lower incidence of hypotension in the general anaesthetic group (OR 1.21 and 95% CI 0.65–2.02).

Table 1 Characteristics of included trials R=regional anaesthesia; G= general anaesthesia; N/A= not available

Trial	Country	Mean age (years) R/G	Gender % female	Number of patients R/G	Methodology score
Adams 1990[8]	Germany	81/79	82	24/32	2
Berggren 1987[9]	Sweden	77/78	81	28/29	7
Bigler[10]	Not stated	80/78	82	20/20	7
Bredahl 1991[11]	Denmark	80/79	100	15/13	6
Brichant 1995[12]	Belgium	N/A	N/A	54/52	4
Brown 1994[13]	Hong Kong	75/79	50	10/10	6
Couderc 1977[14]	France	86	86	50/50	4
Davis 1981[16]	New Zealand	81/78	85	64/68	7
Davis 1987[15]	New Zealand	79.5	78	259/279	6
Maurette 1988[18]	France	81/84	N/A	19/16	6
McKenzie 1984[20]	England	75/74	N/A	73/75	6
McLaren 1978[22]	England	79/76	N/A	26/29	4
Racle 1986[23]	France	82/82	100	35/35	7
Tasker 1983[24]	England	N/A	N/A	100	2
Valentin 1986[25]	Denmark	79	80	251/297	7

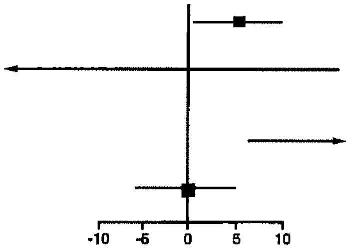
Table 2 Comparison of outcome between regional and general anaesthesia for dichotomous variables. All results were derived using fixed effects analysis except those marked * which were derived using random effects analysis Statistically significant results are indicated by +. Results to the left of the vertical line indicate an advantage for regional anaesthesia over general anaesthesia and conversely for those lying to the right. Results show the incidence of each outcome measure T=number of trials; P=number of patients; OR=odds ratio; CI=confidence intervals

Outcome	T/P	Incidence (regional)	Incidence (general)	Peto OR (95% CI)
Mortality—1 month	7/1578	49/766 (6.4%)	76/812 (9.4%)	0.66 (0.47–0.96)
Mortality—3 months	6/1491	88/726 (12.1%)	98/765 (12.8%)	0.91 (0.67–1.24)
Mortality—6 months	3/1264	103/613 (16.8%)	105/651 (16.1%)	1.05 (0.78–1.41)
Mortality—12 months	2/726	80/354 (22.5%)	78/372 (21.0%)	1.10 (0.77–1.57)
Operative hypotension	7/873	146/426 (34.3%)	116/447 (26.0%)	1.51 (1.12–2.02)+ 1.21 (0.65–2.25)*
Patients receiving transfusion	3/228	63/108 (58.3%)	68/120 (56.7%)	1.02 (0.58–1.80)
Post-operative hypoxia	1/57	10/28 (35.7%)	14/29 (48.3%)	0.60 (0.21–1.71)
Pneumonia	8/1096	27/529 (5.1%)	31/567 (5.5%)	0.92 (0.53–1.59)
Myocardial infarction	4/888	4/431 (0.9%)	8/457 (1.8%)	0.51 (0.16–1.63)
Cerebrovascular accident	7/1085	10/529 (1.9%)	6/556 (1.1%)	1.72 (0.64–4.63)
Congestive cardiac failure	6/902	11/439 (2.5%)	12/463 (2.6%)	0.97 (0.42–2.23)
Renal failure	4/796	2/382 (0.5%)	3/414 (0.7%)	0.77 (0.13–4.50)
Acute confusional state	3/167	10/83 (12.0%)	19/84 (22.6%)	0.47 (0.21–1.06)
Urine retention	2/97	10/48 (20.8%)	10/49 (20.4%)	1.02 (0.39–2.71)
Nausea and vomiting	2/95	2/46 (4.3%)	3/49 (6.1%)	0.69 (0.12–4.13)
Deep vein thrombosis	4/259	39/129 (30.2%)	61/130 (46.9%)	0.41 (0.23–0.72)+
Pulmonary embolism	9/1184	8/575 (1.4%)	10/609 (1.6%)	0.84 (0.33–2.13)



There was marked heterogeneity of values for blood loss and volumes of blood transfused. Three studies[11 16 25] reported an increased operative blood loss for general anaesthesia whilst two studies[8 20] reported an increase for regional anaesthesia. Pooling of results was possible for only three studies,[11 16 20] demonstrating a tendency to an increased blood loss with general anaesthesia (weighted mean difference 81 ml, 95% CI 216–53 ml). Three studies[8 10 16] reported on the number of patients requiring transfusion with no significant difference between anaes-

Table 3 Comparison of outcome between regional and general anaesthesia for continuous variables. All results were derived using fixed effects analysis except those marked * which were derived using random effects analysis. Statistically significant results are indicated by + Results to the left of the vertical line indicate an advantage for regional anaesthesia over general anaesthesia and conversely for those lying to the right T=number of trials; P=number of patients; WMD=weighted mean difference. CI=confidence intervals

Outcome	T/P	Regional	General	WMD (95% CI)	WMD (95% CI)
Length of operation (min)	6/376	189	187		4 82 (1.08–8 56)*
Blood loss (ml)	3/308	152	6		64.6 (–138.5 to 9 3) 81 2 (–216 0 to 53.4)+
Transfusion (ml)	2/218	103	100		168.9 (98.5 to 239.4)
Length of hospital stay (days, additive)	2/218	108	10		–0.21 (–5.21 to 4 78)

thetic methods (63/108 (58%) for general anaesthesia compared with 68/120 (57%) for regional anaesthesia, (Peto OR 1.01, 95% CI 0.6–1.8). Three studies reported this outcome as mean volume of blood transfused.[14,18,23] Two studies[14,23] showed no significant difference but in one study patients who had a regional anaesthetic had twice the mean volume of blood transfused.[18]

Deep vein thrombosis was specifically recorded in one study,[12] in a subgroup of patients in two further studies,[16,20] and mentioned in one further study.[22] Summation of these four studies gave a reduced incidence for regional anaesthesia: 39/129 (30%) for regional anaesthesia compared with 61/120 (51%) for general anaesthesia (Peto OR 0.41, 95% CI 0.23–0.72). Pulmonary embolism was reported in nine studies.[8–10,12,15,16,20,22,23] Summation of all results showed no difference in incidence between the regional and general anaesthetic groups (8/575 (1.3%) for regional anaesthesia compared with 10/609 (1.6%) for general anaesthesia). However, subdivision of the results into fatal and non-fatal embolism showed a significant reduction in incidence of fatal pulmonary embolism following regional anaesthesia.

Data for many morbidities such as pneumonia, congestive cardiac failure, myocardial infarction and cerebrovascular accident were only available as causes of death in some of the trial reports. The incidence of pneumonia (including aspiration pneumonia) was given in eight studies,[8–10,15,16,20,22,23] congestive cardiac failure in six studies,[8–10,15,16,22] renal failure in four studies,[8,15,16,23] urine retention in two studies[9,13] and vomiting in two studies.[10,22] For all these outcomes there was no tendency to any difference between anaesthetic techniques. Myocardial infarction was reported in four studies[15,16,20,23] and confusional states in three studies.[9,10,23] These outcomes had a tendency to be more common after general anaesthesia, but the results did not reach statistical significance. Cerebrovascular accident was reported in seven studies[9,10,14–16,20,23] with a tendency for this complication to be more common after regional anaesthesia, but again the result did not reach statistical significance.

Post-operative arterial oxygen tension was reported in six studies.[9,13–15,20,22] Three of these[13,16,20] reported lower oxygen tension in the immediate post-operative period after general anaesthesia in comparison to regional anaesthesia. The other three[9,14,22] reported no significant difference between techniques. Pooling of data was not possible due to the varying methods of presenting outcomes. Stress hormones were measured in two studies [8,24] both of which reported greater increases after general anaesthesia. Time to ambulation was only recorded in two studies,[10,24] one of which showed no difference between the groups[24] whilst the other[10] noted a reduction in the time to ambulation of 5.1 days in the general anaesthetic group to 3.3 days for regional anaesthesia. Summation of the five studies which reported length of hospital stay showed no difference between the two groups.[8,9,15,20,23] Maurette and colleagues[18] showed no differences between the groups on psychological evaluation and Bredahl and coworkers[11] showed no difference in intra-operative temperature between the groups, although more patients had a core temperature in recovery of <36°C in the spinal group (47% *vs* 23% in the general anaesthesia group).

Complications specific to the method of treatment were only very infrequently detailed (two cases of aspiration pneumonia[16] and one case of headache[10] after spinal anaesthesia). No study reported on differences in final functional outcomes.

Discussion

The present study has pooled the results from over 2000 patients who had either a regional or general anaesthetic for their hip fracture surgery. Many of the included studies involved only small numbers of patients and reported only limited outcome measures. Using data summation, however, it has been possible to derive results showing a significant advantage for regional anaesthetic over general anaesthetic in terms of the incidence of deep vein thrombosis and survival at one month. Surgery for hip fracture is performed in elderly patients who have multiple co-morbidities. It is not therefore surprising that a survival advantage for any anaesthetic technique does not extend into the long term. The result for deep vein thrombosis must be treated with caution as the analysis includes some sub-group data which could lead to bias. This result does, however, correlate with the finding in the previous meta-analysis[3] that deep vein thrombosis was more likely in patients who had received a general anaesthetic.

The reduced incidence of venous thromboembolism following regional anaesthesia has been described following elective hip replacement.[30,31] Several mechanisms may be responsible. The reduction in sympathetic tone to the lower limbs during regional anaesthesia causes an increased venous blood flow[32] which may reduce venous stagnation. It has also been shown that regional anaesthesia is associated with alterations in the viscosity[33] and coagulability of the blood,[34,35] possibly as a result of modifications to the neurohumoral and metabolic responses to surgery.

In the present study there is limited evidence for a reduced incidence in venous thromboembolism following regional anaesthesia. Most of the cases of deep vein thrombosis in this study were from trials using routine venography. The high reported incidence of thrombi (30% for the spinal group and 47% for the general anaesthetic group) does not reflect the clinical rate, which is lower than that detected using radiographic methods. These results do, however, suggest that regional anaesthesia does reduce the risk of major thromboembolic complications following hip fracture surgery.

Although the results represent a sub-group analysis, the finding of a statistically significant reduction in the incidence of fatal pulmonary embolism following regional anaesthesia further suggests that regional anaesthesia may have a protective effect against major thromboembolism. The use of thromboembolism prophylaxis was mentioned in three studies[8,12,13] but not in seven others.[9,10,15,16,20,22,23] Its routine use might negate any benefit of regional anaesthesia in this respect.

General anaesthesia was associated with a small but statistically significant reduction in the length of the operation. There was also a non-significant reduction in the incidence of cerebrovascular accident and the incidence of intra-operative hypotension. As described above, the loss of venous tone during regional anaesthesia is associated with a reduction in blood pressure. It could be postulated that the tendency for a reduced incidence of cerebrovascular accident after general anaesthesia is a consequence of a more stable perioperative blood pressure. The more judicious use of intravenous fluid therapy and vasoconstrictor agents during regional anaesthesia may reduce the advantage of general anaesthesia in this respect.

It has previously been suggested that general anaesthesia induces more postoperative confusion than regional anaesthesia, presumably due to the central nervous system effect of anaesthetic and analgesic drugs. In this study, there was only a non-significant tendency for a greater incidence of confusion following general anaesthesia. Data for other complications were limited, but suggests that there was no difference between the anaesthetic groups for the incidence of pneumonia, urinary retention, congestive cardiac failure and postoperative nausea and vomiting.

This meta-analysis of randomized trials has shown that regional anaesthesia for hip fracture surgery is associated with a reduced early mortality and incidence of deep vein thrombosis in comparison with general anaesthesia. General anaesthesia appears to confer no advantages other than a small reduction in surgical times. Regional anaesthesia should therefore be considered to have marginal advantages, but further randomised trials are justified to elucidate these differences. Such studies should include a protocol for the reduction of hypotension following a regional anaesthetic technique, and full reporting of all outcome measures. This meta-analysis is also published in the Cochrane Library[5] where it will be periodically updated to include new data when available.

Acknowledgements

The authors would like to thank H. Handoll at the Department of Orthopaedic Surgery, Princess Margaret Rose Hospital, Edinburgh for initial study identification, independent data checks and constructive criticism during preparation of the final manuscript and Dr B. Appadu for data collection in the early stages of the study.

References

1 Melton LJ. Hip fractures: a world-wide problem today and tomorrow. *Bone* 1993; **14** (Suppl. 1): S1–8

2 Parker MJ, Pryor GA. *Hip Fracture Management.* Oxford: Blackwell Scientific Publications, 1993

3 Sorenson RM, Pace NL. Anesthetic techniques during surgical repair of femoral neck fracture: a meta-analysis. *Anesthesiology* 1992; **77**. 1095–104

4 Covert CR, Fox GS. Anaesthesia for hip surgery in the elderly. *Can J Anaesth* 1989; **36**: 311–19

5 Cochrane database of systematic reviews. Update Software, PO Box 696, Oxford OX2 7YX, UK

6 Dickerson K, Schere R, Lefebre C. Identifying relevant studies for systemic review. *Br Med J* 1994; **309**: 1286–91

7 *Review manager: version 3.1 for Windows* Oxford. Cochrane Collaboration, 1998

8 Adams HA, Wolf C, Michaelis G, Hempelmann G. Postoperative course and endocrine response of geriatric patients with fractured neck of femur. *Anaesth Intensivther Notfallmed* 1990; **25**: 263–70

9 Berggren D, Gustafson Y, Erikkson B, Bucht G, Hansson LI, Reiz S, Winblad B. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. *Anesth Analg* 1987; **66**: 497–504

10 Bigler D. Adelhoj B, Petring OU, Pederson NO, Busch P, Kalhe P. Mental function and morbidity after acute hip surgery during spinal and general anaesthesia. *Anaesthesia* 1985; **40:** 672–6

11 Bredahl C, Hindsholm KB, Frandsen PC. Changes in body heat during hip fracture surgery: a comparison of spinal and general anaesthesia. *Acta Anaesthesiol Scand* 1991; **35**: 548–52

12 Brichant JF, Blom-Peters L, Buffels R, Lamy M. Central neural blockade failed to decrease deep vein thrombosis in patients undergoing hip surgery and receiving low molecular weight heparin. *Br J Anaesth* 1995; **74**: 75

13 Brown AG, Visram AR, Jones RDM, Irwin MG, Bacon-Shone J.

Preoperative and postoperative oxygen saturation in the elderly following spinal or general anaesthesia – An audit of current practice. *Anaesth Intens Care* 1994; **22**: 150–4

14 Couderc E, Mange F, Duvaldestin P, Desmonts JM. Comparison of outcomes following general or regional anaesthesia in the elderly undergoing surgery for fractured hips. *Anaesth Analg Reanim* 1977; **34**: 987–98

15 Davis FM, Woolner DF, Frampton C, *et al.* Prospective, multicentre trial of mortality following general or spinal anaesthesia for hip fracture in the elderly *Br J Anaesth* 1987; **59**: 1080–8

16 Davis FM, Laurenson VG Spinal anaesthesia or general anaesthesia for emergency hip surgery in elderly patients. *Anaesth Intens Care* 1981; **9**: 352–8

17 Davis FM, Quince M, Larenson VG. Deep vein thrombosis and anaesthetic technique in emergency hip surgery (letter) *Br Med J* 1980, **281**: 1528–9

18 Maurette P,Castagnera L, Vivier C, Erny P Comparative repercussions of general and spinal anaesthesia on the physiological functions of the aged subject. *Ann Fr Anesth Reanim* 1988; **7**: 305–8

19 McKenzie PJ, Wishart HY, Gray I, Smith G. Effects of anaesthetic technique in deep vein thrombosis. A comparison of subarachnoid and general anaesthesia. *Br J Anaesth* 1985; **57**. 853–7

20 McKenzie PJ, Wishart HY, Smith G. Long-term outcome after repair of fractured neck of femur. Comparison of general and spinal anaesthesia. *Br J Anaesth* 1984; **56**: 581–5

21 McKenzie PJ, Wishart HY, Dewar KMS, Gray I, Smith G. Comparison of the effects of spinal anaesthesia and general anaesthesia on postoperative oxygenation and perioperative mortality. *Br J Anaesth* 1980, **52**. 49–54.

22 McLaren AD, Stockwell MC, Reid VT. Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of spinal and general anaesthesia in the elderly *Anaesthesia* 1978; **33**: 10–14

23 Racle JP, Benkhadra A, Poy JY, Gleizal B, Gaudray A. Comparative study of general and spinal anaesthesia in elderly women in hip surgery. *Ann Fr Anesth Reanim* 1986; **5**: 24–30

24 Tasker TPB, Raitt DG, Kohn RLJ, Vater M, Crawshaw C. Subarachnoid block or general anaesthesia?: a study of the stress response during and after surgery for prosthetic replacement of fractured neck of femur. *J Bone Joint Surg* 1983; **65**: 660

25 Valentin N, Lombolt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anaesthesia for surgery of the fractured hip? A prospective study of mortality in 578 patients. *Br J Anaesth* 1986; **58**: 284–91

26 White JWC, Chappell WA. Anaesthesia for surgical correction of fractured femoral neck. A comparison of three techniques. *Anaesthesia* 1980; **35**: 1107–10

27 Wickstrom I, Homberg I, Stefansson T. Survival of female geriatric patients after hip fracture surgery. A comparison of 5 anaesthetic methods. *Acta Anaesthesiol Scand* 1982; **26**: 607–14

28 Tonzcar L, Hammerle AF The impairment of stress parameters by hip joint close operations and the influence of anaesthesia. Preliminary results of a prospective study. *Unfallchirurgie* 1981, **7**: 138–141

29 Darling JR, Murray JM, Hainsworth AM, Trinick TR. The effect of isoflurane or spinal anaesthesia on indocyanine green disappearance in the elderly. *Anesth Analg* 1994; **78**: 706–9

30 Modig J, Hjelmstedt A, Sahlstedt B, Maripuu E. Comparative influences of epidural and general anaesthesia on deep vein thrombosis and pulmonary embolism after total hip replacement *Acta Chirugica Scand* 1981; **147** 125–30

31 Thorburn J, Louden JR, Vallance R. Spinal and general anaesthesia in total hip replacement: frequency of deep vein thrombosis *Br J Anaesth* 1980; **52**: 1117

32 Shimosato S, Etston BE. The role of the venous system in cardiocirculatory dynamics during spinal and epidural anesthesia in man. *Anesthesiology* 1969; **43**: 619–628

33 Drummond AR, Drummond MM, McKenzie PJ, *et al* The effects of general and spinal anaesthesia on red cell deformability and blood viscosity in patients undergoing surgery for fractured neck of femur. In: Stolz JF, Drouin P, eds. *Haemorheology and Diseases.* Paris: Doin Editeurs, 1980

34 Modig J, Borg T, Bagge L, Saldeen T. Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement. *Br J Anaesth* 1983; **55**: 625

35 Simpson PJ, Radford SG, Forster SJ, Cooper GM, Hughes AO The fibrinolytic effects of anaesthesia. *Anaesthesia* 1982; **37**: 3

British Journal of Anaesthesia 84 (4): 456–8 (2000)

Novel bioadhesive delivery system for percutaneous local anaesthesia

D. F. McCafferty*, A. D. Woolfson and G. P. Moss[1]

School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, UK. [1]*Unilever Research, Port Sunlight Laboratory, Quarry Road East, Bebington, Wirral, Merseyside L63 3JW, UK*

**Corresponding author*

We have assessed the efficacy of a novel bioadhesive amethocaine patch device, compared to Ametop™ gel, in a randomized, double-blinded trial. Patch and gel formulations, including placebos, were applied to the forearms of volunteers (n=30) for 40 min. Once the formulations were removed from the skin, anaesthesia was assessed by volunteers using a conventional pin-prick test. Pain scores were recorded for 4 h after removal of gels and patches. Statistical analysis of the results indicated that both amethocaine gel and patch preparations were superior to placebo ($P<0.05$). No significant difference was observed between amethocaine gel and patch formulations ($P>0.05$) in either onset time or duration of action for percutaneous local anaesthesia. The results of this study indicate therefore that the novel bioadhesive patch provides clinically comparable anaesthesia to the established gel formulation in a more defined dosage form.

Br J Anaesth 2000; **84**: 456–8

Keywords: anaesthetics, local; methodology

Accepted for publication: September 13, 1999

There are two products available in the UK for provision of topical anaesthesia, EMLA® cream and Ametop™ gel. The former is based on a eutectic mixture of the amide local anaesthetics lidocaine and prilocaine (2.5% w/w of each anaesthetic), while Ametop™ contains 4% w/w amethocaine in a hydrophilic gel. Several clinical studies have recently compared the efficacy of EMLA® and Ametop™, indicating that Ametop™ gel provides a more rapid onset time and a greater duration of anaesthesia than EMLA® cream.[1–4] This has been attributed to the use of the amethocaine phase-change system by Ametop™ gel. In this system, the water in the gel forms a meta-stable hydrate with amethocaine and lowers the melting point of the drug from 42°C to ~30°C.[5 6] Therefore, when Ametop™ gel is applied to intact skin a phase change occurs whereby solid particles of amethocaine convert into highly penetrative oil globules.

Although gel systems are relatively simple to manufacture and use, they can be inconvenient in certain situations, for example, where the mass of gel to be applied is large or where a specific region on the skin such as a port-wine stain needs to be treated accurately.[7] The formulation and clinical assessment of a hydrophilic amethocaine-containing patch device for percutaneous local anaesthesia has been previously described.[8] The patch device described produced comparable skin anaesthesia to amethocaine gel formulations. However, the film was non-adhesive and was secured to the skin by means of a pressure-sensitive island dressing, which was complex in design and difficult to make.

The formulation and characterization of an integrated, moisture-activated, bioadhesive amethocaine patch for percutaneous local anaesthesia has been recently reported.[9] While this device also employs the amethocaine phase-change system, it does not require further surrounding adhesive dressings, as it is formulated to incorporate a bioadhesive co-polymer.[5] This device is relatively simple to make and the patch has the advantage of being removed easily from skin by peeling without leaving a residue.

The amethocaine phase-change system has to date provided the most clinically successful method for delivery of percutaneous local anaesthesia. Therefore, the aim of this study was to evaluate, in a randomized, double-blinded cross-over study, the clinical effectiveness of an integrated, water-activated bioadhesive patch device based on the amethocaine phase-change system by comparing it with the established Ametop™ gel.[5]

Materials and methods

Bioadhesive amethocaine patches were prepared from gels containing 1% w/w amethocaine, as described previously.[9] Placebo patches were similarly prepared. Both patches

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

were presented in heat-sealed pouches. Ametop$^{\text{TM}}$ gel was supplied by Smith & Nephew. A placebo gel was also prepared to match the active formulation. Both gels were packaged into standard lacquered aluminium tubes, using conventional pharmaceutical methods.

Upon obtaining Ethical Committee approval, 30 volunteers (16 female, 20–22 yr) were recruited for the trial. All volunteers completed the study.

Double-blinding of the study was carried out by randomly allocating each formulation a code. Gels (1 g containing amethocaine 40 mg and placebo gel) and patches (3 × 3 cm, containing amethocaine 40.5 mg and placebo patch) were applied to the ventral surface of the forearm; gels (covering an area of 9 cm^2) were covered with a standard dressing. Patches were moistened for 10 s and then placed upon the ventral surface of the forearm of the volunteer whereupon a bioadhesive bond was formed. All volunteers received each of the four formulations (active gel and patch, placebo gel and patch) on four separate occasions. A period of 7 days was observed between administration of formulations. Each formulation was left on the forearm for 40 min. The formulation was then removed and the treated site wiped clean. The volunteers were instructed to prick the site six times, using a sterile Microlance 25G5/8, in a random fashion[10, 11] and, thereafter, the evoked pain was recorded on a four-point scale (1 = no pain; 2 = slight sensation; 3 = moderate pain; 4 = no apparent anaesthesia). Pain scores were assessed by each volunteer, at the specified time periods, after patch or gel removal. Pain scores were recorded and the mean score at each time period was determined. Volunteers were also encouraged to comment upon any aspect of the dosage form or the trial they desired.

Data from each volunteer were collated after the trial and analysed by application of a two-way analysis of variance (ANOVA) with repeated measures. Further analysis was carried out by performing a Fisher exact test for the mean. A significance level of 5% was chosen in all tests.[8, 9]

Pain scores obtained for Ametop$^{\text{TM}}$ gel and the amethocaine patch, at each time point, were compared statistically using the chi-square method with a 2 × 2 contingency table and employing a continuity correction.

Power was estimated using an approximate two-sample *t*-test, using the means and standard deviations for the gel and bioadhesive patch at each time point. Overall, the power was estimated at ~90% to detect a difference of 1 in the pain scores.

Results

Analysis of variance showed that there was a significant difference between the formulations ($P<0.05$). This was determined, upon further analysis, to be because of the inclusion of the placebo preparations. Analysis of the combined pain scores throughout the duration of the self-assessment period showed that with Ametop$^{\text{TM}}$ gel 84.4% of the volunteers had a pain score of 1, compared with 80.3% of those with a bioadhesive amethocaine patch. Both placebos yielded the maximum pain score of 4. Statistical analysis using the Fisher exact test indicated that there was no significant difference between the placebo gel and patch formulations over the entire time period of the study ($P>0.05$). There was a significant difference ($P<0.05$) between placebo and active formulations. There was no significant difference ($P>0.05$) between the amethocaine gel and patch formulations. Table 1 illustrates the distribution of pain scores 1 and 2 for Ametop$^{\text{TM}}$ gel and the amethocaine patch (there were no reported pain scores of 3 or 4, for either active formulation, during the course of the study).

Table 1 Percentage of pain scores (1 or 2) for active formulations at each point of pain assessment

Time (min)	Ametop$^{\text{TM}}$ gel % pain score		Patch % pain score	
	1	2	1	2
40	60	40	30	70
45	70	30	50	50
50	73	27	60	40
55	80	20	73	27
60	100	0	80	20
75	100	0	100	0
90	100	0	100	0
120	100	0	100	0
150	100	0	100	0
180	80	20	100	0
210	80	20	90	10
240	67	33	80	20

Statistical analyses of the pain scores obtained at each time point indicated that there was no significant difference ($P>0.5$) between Ametop$^{\text{TM}}$ gel and the amethocaine patch.

Discussion

There are a number of potential advantages in designing a bioadhesive patch device for providing percutaneous local anaesthesia. Each patch will have a specific amount of drug applied to a clearly defined area; this is not possible when using gels or creams. Furthermore, application and removal of the device are potentially easier as gels and creams require a covering to protect them from removal from the skin surface. This covering needs to be removed prior to wiping such formulations from the surface of the skin. Removal of the covering, normally a pressure-sensitive adhesive dressing, can also be quite a painful procedure. Although a previous amethocaine patch device has been described, it was not bioadhesive and required a dressing to maintain skin contact.

The results of the study clearly demonstrated the differences between active and placebo formulations. The mean pain scores for both Ametop$^{\text{TM}}$ gel and the amethocaine patch were less than 2 throughout the assessment period, and statistical analyses of the results indicated that there was no difference in the active preparations. Interestingly, pain scores of 3 and 4 were not reported at any time point and this is in broad agreement with earlier reports on amethocaine-based systems.

The recommended application time for Ametop™ gel is between 30 and 45 min, with the shorter application time being used for children. It has been previously reported that pain scores of either 1 or 2 are classified as clinically effective, and hence both active formulations provided satisfactory percutaneous local anaesthesia.[10] The distribution of pain scores 1 and 2 clearly illustrated that as time progressed the number of pain scores of 1 gradually increased to the point where all volunteers gave this result; this occurred from ~60 to 150 min. It was also observed that pain scores continued to decrease even after removal of the active preparations. This is due to a drug reservoir being present in the stratum corneum so that drug diffusion into underlying tissues continues after removal of the active formulations.[8] After 150 min the number of pain scores of 1 began to decrease while pain scores of 2 increased. Nevertheless, from a clinical viewpoint there was satisfactory percutaneous local anaesthesia in all of the volunteers over the entire period of the study (240 min).

In a recent study,[12] a liposome-encapsulated amethocaine formulation was applied to 40 volunteers for a period of 1 h and anaesthesia was monitored by pin prick. Although volunteers reported a good anaesthetic effect, the formulation failed to provide percutaneous local anaesthesia in 5% of the subjects. Hence, it was suggested that certain individuals may require longer application times. This, perhaps, is not surprising given that the drug must first be released from the liposome before it can produce percutaneous local anaesthesia.

In the present study, no significant side effects were evident. Three volunteers reported slight, transient erythema at the site of application with the amethocaine patch, and two other volunteers reported a similar reaction after application of the amethocaine gel. These findings are in good agreement with the incidence of such reactions in other studies. However, in a recent report[12] concerning percutaneous local anaesthesia using liposome-encapsulated amethocaine, it was stated that 80% of the volunteers exhibited erythema. A possible explanation for this was that a higher concentration of drug was used (5%) and the application time was 1 h.

The results of this study indicate that the water-activated amethocaine patch device produces equivalent anaesthesia to the amethocaine aqueous gel formulation. Therefore, the patch device tested in this study provided a suitable alternative to established gel or cream formulations. In addition, it delivers a specific amount of drug to a specific surface area of skin.

References

1 Khorshid SM, Cerio R. Superficial skin surgery using topical 4% amethocaine gel (Ametop™): a comparison with infiltrated lignocaine. *J Dermatol Treatment* 1997; **8**: 183–7
2 Wongprasartsuk P, Main BJ. Adverse local reactions to amethocaine cream – audit and case reports. *Anaesth Intensive Care* 1998; **26**: 312–4
3 Russell SCS, Doyle E. A risk-benefit assessment of topical percutaneous local anaesthetics in children. *Drug Safety* 1997; **16**: 279–87
4 van Kan HJM, Egberts ACG, Rijnvos WPM, TerPelkwijk NJ, Lenderink AW. Tetracaine versus lidocaine-prilocaine for preventing venepuncture induced pain in children. *Am J Health-System Pharma* 1997; **54**: 388–92
5 McCafferty DF, Woolfson AD. Percutaneous local anaesthetic composition for topical application and associated method. UK Patent 2,163,956, 1988
6 Woolfson AD, McCafferty, DF. Percutaneous local anaesthesia: drug release characteristics of the amethocaine phase-change system. *Int J Pharmaceut* 1993; **94**: 75–80
7 McCafferty DF, Woolfson AD, Handley J, Allen G. Effect of percutaneous local anaesthetics on pain reduction during pulse dye laser treatment of portwine stains. *Br J Anaesth* 1997; **78**: 286–9
8 McCafferty DF, Woolfson AD. New patch delivery system for percutaneous local anaesthesia. *Br J Anaesth* 1993; **71**: 370–4
9 Woolfson AD, McCafferty DF, Moss GP. Development and characterisation of a moisture-activated bioadhesive drug delivery system for percutaneous local anaesthesia. *Int J Pharmaceut* 1998; **169**: 83–94
10 Woolfson AD, McCafferty DF, Boston, V. Clinical experiences with a novel percutaneous amethocaine preparation: prevention of pain due to venepuncture in children. *Br J Clin Pharmacol* 1990; **30**: 273–9
11 Cooper CN, Gerrish SP, Hardwick M, Kay R. EMLA® cream reduces the pain of venepuncture in children. *Eur J Anaesthesiol* 1987; **4**: 441–8
12 Fisher R, Hung O, Mezei M, Stewart R. Topical anaesthesia of intact skin: liposome-encapsulated tetracaine v EMLA. *Br J Anaesth* 1998; **81**: 972–3

British Journal of Anaesthesia **84** (4): 459–62 (2000)

Prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic surgery

J. J. Wang[1]*, S. T. Ho[1], H. S. Liu[2] and C. M. Ho[3]

[1]Department of Anesthesiology, [2]Department of Obstetrics and Gynecology and [3]Institute of Medical Sciences, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

**Corresponding author: Department of Anesthesiology, Tri-Service General Hospital/National Defense Medical Center, No. 8, Sec. 3, Ting-Chow Road, Taipei, Taiwan.*

The aim of this study was to evaluate the prophylactic antiemetic effect of i.v. dexamethasone in women undergoing ambulatory laparoscopic tubal ligation. Ninety patients requiring general anaesthesia for laparoscopic tubal ligation were enrolled in a randomized, double-blind, placebo-controlled study. Forty-five patients received dexamethasone 10 mg i.v. and 45 received saline 2 ml i.v. at the induction of anaesthesia. We found that 27% of patients in the dexamethasone group, compared with 63% of patients in the saline group, reported nausea and vomiting within 4 h after surgery ($P<0.01$). Seven per cent of patients in the dexamethasone group, compared with 28% of patients in the saline group, received a rescue antiemetic ($P<0.05$). During the 24-h postoperative observation period, 34% of patients in the dexamethasone group, compared with 73% of patients in the saline group, reported nausea and vomiting ($P<0.001$). We conclude that dexamethasone 10 mg significantly decreases the incidence of postoperative nausea and vomiting in women undergoing ambulatory laparoscopic tubal ligation.

Br J Anaesth 2000; **84**: 459–62

Keywords: pharmacology; surgery, laparoscopy; vomiting, antiemetics, nausea

Accepted for publication: November 4, 1999

The incidence of nausea and vomiting after outpatient gynaecological laparoscopic surgery is high (54–92%[1–5]). A number of antiemetics have been studied in attempts to decrease the incidence of postoperative nausea and vomiting (PONV) in the ambulatory setting.[1–6] Among the antiemetics used currently, $5HT_3$ antagonists such as ondansetron and granisetron are increasing in popularity. Although these drugs are effective, their high cost limits their widespread use.[3 4] Other antiemetic drugs used currently (e.g. anticholinergics, dopamine receptor antagonists and antihistamines), although effective, possess clinically significant side effects (e.g. restlessness, dry mouth, tachycardia and extrapyramidal symptoms).[6–8] A low-cost antiemetic agent with few side effects would be of benefit to anaesthetists and their patients.

Recently, dexamethasone has been found to have a prophylactic effect on PONV in patients undergoing tonsillectomy,[9 10] thyroidectomy[11] or abdominal hysterectomy.[12 13] Theoretically, it may also be effective in the prevention of PONV in women undergoing ambulatory laparoscopic surgery. The aim of this study was to evaluate the prophylactic antiemetic effect of dexamethasone in women undergoing ambulatory laparoscopic tubal ligation.

Patients and methods

After obtaining institutional review board approval and written informed patient consent, 90 women (ASA I or II), scheduled for outpatient laparoscopic tubal ligation, were enrolled in the study. Patients who were breast-feeding, weighed >90 kg or were taking any medication other than an oral contraceptive pill were excluded.

On arrival in the operating room, routine monitoring devices were placed, and baseline blood pressure, heart rate and pulse oximetry values were recorded. Patients were then randomly assigned to one of two groups ($n = 45$ each) using a computer-generated random number table. Study medications (2 ml) were prepared by one of the investigators and were administered using a double-blind design. At the time of induction, one group of patients received dexamethasone 10 mg i.v. and the other group received saline i.v.

The anaesthetic regimen and surgical procedure were standardized for all patients. Anaesthesia was induced with sodium pentothal 4 mg kg^{-1}, glycopyrrolate 0.2 mg and fentanyl 2 μg kg^{-1}. Tracheal intubation was facilitated with vecuronium 0.15 mg kg^{-1} i.v. and anaesthesia was maintained with 1.0–2.5% (inspired concentration) isoflur-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

ane in oxygen. Ventilation was controlled mechanically and adjusted so as to keep the end-tidal partial pressure of carbon dioxide between 3.9 and 5.2 kPa, using an anaesthetic–respiratory gas analyser (Capnomac Ultima; Datex, Helsinki, Finland). Laparoscopic tubal ligation was performed under video guidance and involved two punctures of the abdomen. During surgery, the patients were placed in the Trendelenburg position and the abdomen was insufflated with carbon dioxide with an intra-abdominal pressure of 1.3–1.8 kPa. At the cessation of the surgery, glycopyrrolate 0.6 mg and neostigmine 3 mg were administered i.v. to reverse the neuromuscular block, and the tracheal tube was removed.

After surgery, the patients were transported to the post-anaesthetic care unit (PACU). During their stay in the PACU (4 h), blood pressure, heart rate and respiratory rate were monitored every 15 min and oxygen saturation (Sa_{O_2}; by pulse oximetry) was monitored continuously. Tenoxicam 20 mg i.v. was given routinely for the prevention of postoperative pain. Pain intensity was assessed using a 10-cm visual analogue scale (VAS; from 0 = no pain to 10 = most severe pain). Because pain after laparoscopic tubal ligation is relatively minor,[21] the patients did not receive further analgesic treatment after discharge.

Nausea and vomiting were assessed immediately after operation and at 1-h intervals for 4 h. In addition, nausea and vomiting were assessed by a telephone interview 24 h after discharge from hospital. Nausea and vomiting were evaluated on a 3-point ordinal scale (0 = none, 1 = nausea, 2 = vomiting). In the present study, no distinction was made between vomiting and retching (i.e. a retching event was considered as a vomiting event). Ondansetron 4 mg i.v. was given on patient request or when vomiting occurred. Both patient and investigator were blinded.

Sample size was predetermined. We expected a 30% difference in the occurrence of nausea and vomiting between groups. The α error was set at 0.05 (two-sided) and the β error at 0.10. The projected sample size was 37 patients for each group. Parametric data were analysed with the unpaired *t* test. Non-parametric data were analysed using the Mann–Whitney *U* test. Categorical data were analysed with the chi-squared test. A *P* value less than 0.05 was considered significant.

Results

Of the 90 patients enrolled in this study, six patients who did not complete the surgical procedure (laparoscopic tubal ligation) because of intra-abdominal adhesions and three patients who could not be contacted by telephone after hospital discharge were eliminated from the study. The data obtained from the remaining 81 patients were analysed. Patient characteristics, interval since the the last menstrual period and the durations of anaesthesia and surgery were similar in the two groups (Table 1).

Table 1 Patient characteristics Values are numbers or medians (range)

Group	Dexamethasone	Saline
n	41	40
Age (yr)	32 (28–36)	34 (31–35)
Weight (kg)	54 (42–73)	56 (46–75)
Height (cm)	157 (138–171)	158 (145–172)
Interval since last menstrual period (days)		
0–8	11	12
9–16	8	8
16–28	12	14
>28	10	6
Duration of anaesthesia (min)	68 (46–78)	65 (51–76)
Duration of surgery (min)	42 (32–61)	46 (38–64)

Table 2 Incidence of nausea and vomiting after laparoscopic tubal ligation Values are numbers of patients (%) PACU = postanaesthetic care unit; NS = not significant. *P value (chi-squared test)

Group	Dexamethasone	Saline	*P**
n	41	40	
In PACU (0–4 h postoperatively)			
Nausea	8 (20%)	14 (35%)	
Vomiting	3 (7%)	11 (28%)	
Total	11 (27%)	25 (63%)	<0.01
After discharge (4–24 h postoperatively)			
Nausea	5 (12%)	8 (20%)	
Vomiting	2 (5%)	4 (10%)	
Total	7 (17%)	12 (30%)	NS
0–24 h postoperatively			
Nausea	10 (24%)	15 (38%)	
Vomiting	4 (10%)	14 (35%)	
Total	14 (34%)	29 (73%)	<0 001

There were no significant differences in blood pressure, heart rate and respiratory rate between groups. No patient demonstrated a Sa_{O_2} below 90%. Patients in the two groups reported a similar, low pain score (VAS: 0–3).

The efficacy of dexamethasone as a prophylactic antiemetic compared with placebo treatment is summarized in Table 2. We used the total incidence of nausea and vomiting to represent PONV. During their stay in the PACU (4 h postoperatively), 27% of patients in the dexamethasone group in comparison with 63% of patients in the saline group reported PONV ($P<0.01$, chi-squared test). Seven per cent of the patients (three patients) in the dexamethasone group, in comparison with 28% of patients (11 patients) in the saline group, needed rescue antiemetic (ondansetron 4 mg i.v.) ($P<0.05$, chi-squared test). During the postoperative observation period of 24 h, 34% of patients in the dexamethasone group in comparison with 73% of patients in the saline group reported PONV ($P<0.001$, chi-squared test).

Discussion

Although the use of laparoscopy for tubal ligation has decreased surgical morbidity and has become a popular procedure for sterile working in an ambulatory setting,[14 15] high incidences of PONV (54–92%) have been reported.[1–5] In our study, we found that the total incidence of PONV was 73% within 24 h postoperatively in patients undergoing laparoscopic tubal ligation when no antiemetic was given prophylactically. After pretreatment with dexamethasone the incidence of PONV was reduced significantly to 34%.

Dexamethasone was first reported as an effective antiemetic in patients receiving cancer chemotherapy in 1981.[16] Since then, several studies have shown that dexamethasone is equal to or better than other antiemetic agents in preventing the nausea and vomiting associated with chemotherapy.[17–19] Recently, dexamethasone has also been reported to be effective in preventing PONV in patients receiving tonsillectomy, thyroidectomy and abdominal hysterectomy.[9–13] Therefore, we hypothesized that dexamethasone might also be effective in the prevention of PONV in women undergoing ambulatory laparoscopic surgery. In the present study, we found that the prophylactic use of dexamethasone significantly reduced the incidence of PONV in women undergoing ambulatory laparoscopic surgery.

Although severe postoperative pain may influence the occurrence of PONV,[8 20] pain after laparoscopic tubal ligation is relatively minor.[21] It is significantly less and of shorter duration than that caused by other lower abdominal surgical procedures, especially laparotomy.[21] After routine administration of a long-acting non-steroid anti-inflammatory drug (tenoxicam 20 mg), patients in the two groups in the present study reported a similar, low pain score of VAS 0–3.

The aetiology of PONV in patients undergoing laparoscopic tubal ligation is not fully understood. Risk factors such as a residual pneumoperitoneum after carbon dioxide insufflation,[22] the intraoperative use of isoflurane, fentanyl or glycopyrrolate,[8 20 22] the occurrence of postoperative pain[8 20] and the phase of the menstrual cycle[5] may all contribute to these episodes. Because any of these factors could have interfered with the interpretation of the result of the study, we controlled for all these factors in the design of the study. All patients underwent laparoscopic tubal ligation with a standardized anaesthetic regimen and surgical procedure. The durations of anaesthesia and surgery and the anaesthetics used were similar in the two groups. In addition, the phase of the menstrual cycle and the intensity of postoperative pain were also similar between the groups. Therefore, it is likely that the differences in the incidence of PONV between groups are attributable to dexamethasone rather than to any confounding variable.

The exact mechanism by which dexamethasone exerts its antiemetic action is not known. Glucocorticoids have been shown to have various effects on the central nervous system. They regulate neurotransmitter concentrations, receptor densities, signal transduction and neuron configuration.[23 24] Numerous glucocorticoid receptors are found in the nucleus of the solitary tract, the raphe nucleus and the area postrema.[24 25] These nuclei are known to have significant neuronal activity in the regulation of the nausea and vomiting reflex.[8 26] Dexamethasone may exerts its antiemetic action through these nuclei.

A wide range of doses of dexamethasone (8–32 mg) has been used in the management of the PONV and emesis associated with chemotherapy.[9–13 17–19] Among these doses, 8–10 mg has been used most frequently in the prevention of PONV.[9–13] Therefore, a 10-mg dose was chosen for the present study. Although it might not be the optimal dose, dexamethasone 10 mg significantly decreased the incidence of PONV in women undergoing ambulatory laparoscopic surgery. Dose–response studies, however, will be necessary in the future to determine the optimal dose of dexamethasone for the prevention of PONV in patients receiving laparoscopic tubal ligation.

Long-term corticosteroid therapy may have significant morbidity. However, side-effects from brief (24–48 h), even high-dose, corticosteroid treatment have been rare. After conducting an extensive literature search, we were unable to find a report of side-effects associated with the use of a single dose of dexamethasone. Although a single dose of dexamethasone is considered safe,[9–13] further study is indicated.

Acknowledgements

This work was supported in part by grant NSC89-2314-B-016-060 from the National Council of Science, Taiwan

References

1 Bodner M, White PF. Antiemetic efficacy of ondansetron after outpatient laparoscopy. *Anesth Analg* 1991; **73**: 250–4

2 Pandit SK, Kothary SP, Pandit UA, Randel G, Levy L. Dose–response study of droperidol and metoclopramide as antiemetics for outpatient anaesthesia. *Anesth Analg* 1989; **68**: 798–802

3 Sniadach MS, Alberts MS. A comparison of the prophylactic antiemetic effect of ondansetron and droperidol on patients undergoing gynecologic laparoscopy. *Anesth Analg* 1997; **85**: 797–800

4 Raphael JH, Norton AC. Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: randomized, double-blind comparison with metoclopramide. *Br J Anaesth* 1993; **71**: 845–8

5 Honkavaara PH, Lehtinen AM, Hovorka J, Korttila K. Nausea and vomiting after gynaecological laparoscopy depends upon the phase of menstrual cycle. *Can J Anaesth* 1991, **38**: 876–9

6 Melnick B, Sawyer R, Karambelkar D, Phitayakorn P, Lim NT, Patel R. Delayed side effects of droperidol after ambulatory general anesthesia. *Anesth Analg* 1989; **69**: 748–51

7 Jiménez-Jiménez FJ, Garcia-Ruiz PJ, Molina JA. Drug-induced movement disorders. *Drug Safety* 1997; **16**: 180–204

8 Watcha MF, White PF. Postoperative nausea and vomiting. Its etiology, treatment and prevention. *Anesthesiology* 1992; **77**: 162–184

9 Pappas ALS, Sukhani R, Hotaling AJ, Mikat-Stevens M, Javorski JJ, Donzelli J, Senoy K. The effect of preoperative dexamethasone on the immediate and delayed postoperative morbidity in children undergoing adenotonsillectomy. *Anesth Analg* 1998, **87**: 57–61

10 Splinter WM, Roberts DJ. Prophylaxis for vomiting by children after tonsillectomy: dexamethasone versus perphenazine. *Anesth Analg* 1997; **85**: 534–7

11 Wang JJ, Ho ST, Lee SC, Liu YC, Liu YH, Liao YC. The prophylactic effect of dexamethasone on postoperative nausea and vomiting in women undergoing thyroidectomy: a comparison of droperidol with saline. *Anesth Analg* 1999, **89**: 200–3

12 Fujii Y, Tanaka H, Toyooka H. The effects of dexamethasone on antiemetics in female patients undergoing gynecologic surgery. *Anesth Analg* 1997; **85**: 913–7

13 López-Olaondo LL, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Sáez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. *Br J Anaesth* 1996; **76**: 835–40

14 Wilson EW. The evolution of methods for female sterilization. *Int J Gynecol Obstet* 1995; **1**: 3–13

15 World Health Organization. Minilaparotomy or laparoscopy for sterilization: a multicenter, multinational randomized study. *Am J Obstet Gynecol* 1982; **143**: 645–52

16 Aapro MS, Alberts DS. Dexamethasone as an antiemetic in patients treated with cisplatin [letter]. *N Engl J Med* 1981; **305**: 520

17 Sehine I, Nishiwaki Y, Kakinuma R, Kubota K, Hojo F, Matsumoto T, Ohmatsu H, Yokozaki M, Goto K, Miyamoto T, Takafuji J, Kodama T. Phase II study of high-dose dexamethasone-based association in acute and delayed high-dose cisplatin-induced emesis–JCOG study 9413. *Br J Cancer* 1997; **76**: 90–2

18 Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. *N Engl J Med* 1995; **332**: 1–5

19 Italian Group for Antiemetic Research. Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis. *J Clin Oncol* 1997; **15**: 124–30

20 Cohen MM, Duncan PG, DeBoer DP, Tweed WA. The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth Analg* 1994; **78**: 7–16

21 Alexander JI. Pain after laparoscopy. *Br J Anaesth* 1997; **79**: 369–78

22 Fredman B, Jedeikin R, Olsfanger D, Flor P, Gruzman A. Residual pneumoperitoneum: a cause of postoperative pain after laparoscopic cholecystectomy. *Anesth Analg* 1994; **79**: 152–4

23 Schimmer BP, Parker KL. Adrenocorticotropic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, eds. *Goodman and Gillman's the Pharmacological Basis of Therapeutics*, 9th edn. New York: McGraw-Hill, 1996; 1459–86

24 Morimoto M, Morita N, Ozawa H, Yokoyama K, Kawata M. Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and *in situ* hybridization study. *Neurosci Res* 1996; **26**: 235–69

25 Funder JW. Mineralocorticoid receptors and glucocorticoid receptors. *Clin Endocrinol* 1996; **45**: 651–6

26 Naylor RJ, Inall FC. The physiology and pharmacology of postoperative nausea and vomiting. *Anaesthesia* 1994; **49**: 2–5

British Journal of Anaesthesia **84** (4). 463–7 (2000)

Acupressure and prevention of nausea and vomiting during and after spinal anaesthesia for Caesarean section

D. Harmon[1]*, M. Ryan[1], A. Kelly[2] and M. Bowen[3]

[1]*Department of Anaesthesia, Rotunda Hospital, Dublin, Ireland.* [2]*Department of Community Health and General Practice, Trinity College, Dublin, Ireland.* [3]*Department of Anaesthesia, Rotunda Hospital, Dublin, Ireland*

**Corresponding author: Department of Anaesthesia, University College Hospital, Galway, Ireland*

The efficacy of acupressure at the P6 point in the prevention of nausea and vomiting during and after Caesarean section was studied. A double-blind, randomized controlled study of acupressure *vs* placebo was designed. Ninety-four patients scheduled for Caesarean section were included. The anaesthetic technique and postoperative analgesia were standardized. The use of acupressure reduced the incidence of nausea or vomiting from 53% to 23% compared with placebo (95% confidence interval (CI) 0.34–0.25; $P=0.002$) during the operation and from 66% to 36% compared with placebo (95% CI 0.34–0.19; $P=0.003$) after the operation. Other variables were similar between the groups.

Br J Anaesth 2000; **84**: 463–7

Keywords: acupressure; anaesthesia, obstetric; vomiting, nausea

Accepted for publication: October 6, 1999

Most mothers request and receive regional anaesthesia for Caesarean section. Nausea and vomiting are important side effects both during and after Caesarean section under spinal anaesthesia. They may distress the patient and decrease overall satisfaction with pain relief. Rowbotham, in his review of the management of postoperative nausea and vomiting (PONV), concluded that the efficacy of currently available anti-emetics remains poor.[1] Routine use of anti-emetic drugs in patients during Caesarean section is not recommended by many because of adverse effects.

Many factors influence nausea and vomiting both during and after Caesarean section, and these must be carefully controlled when studying PONV.[2] The aetiology of emetic symptoms during and after operations tends to differ. Caesarean section under spinal anaesthesia is associated with maternal nausea in up to 80% of patients not premedicated with a pharmacological anti-emetic.[3] There is also a high incidence (56%) of postoperative nausea and vomiting in this setting.[4]

Acupressure, a non-invasive variation of acupuncture, has been reported as a potential non-pharmacological method of preventing nausea and vomiting. In acupressure, manual stimulation is applied, whereas in acupuncture the skin is pierced with a needle. Studies have shown that acupressure can decrease the nausea due to morning sickness,[5] general anaesthesia,[6] chemotherapy[7] and motion sickness.[8] Other studies of this technique which had unfavourable results include those by Yentis and Bissonnette[9] and Lewis and colleagues.[10]

Acupressure has been shown to be effective in the prevention of nausea and vomiting during spinal anaesthesia for Caesarean section, including intrathecal fentanyl.[11] This study, by Stein and colleagues, is limited, as nausea and vomiting were recorded only during operations. Efficacy after spinal anaesthesia was not studied. Factors predisposing to nausea and vomiting during spinal anaesthesia for Caesarean section differ from those after operation.

Intrathecal fentanyl for postoperative analgesia is limited by its short duration of action with single bolus administration.[12] Spinal anaesthesia including intrathecal morphine provides prolonged and effective analgesia after operations.[13] We therefore investigated the effect of acupressure on nausea and vomiting during and after operations in patients undergoing Caesarean section under bupivacaine/morphine spinal anaesthesia.

Methods

A prospective, randomized, double-blind study was designed and approval was obtained from the hospital's ethics and research committee. Written informed consent was obtained from all patients. The study was designed with a power of 0.9, to detect a 30% difference in the incidence of nausea and vomiting, with a significance level of 0.05. This required the recruitment of 94 patients.

Patients, ASA I, aged between 18 and 40 yr scheduled for elective Caesarean section were recruited. Those with a previous history of PONV or nausea and vomiting in the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

preceding 24 h, obesity (BMI >35), diabetes mellitus or previous experience of acupuncture or acupressure were excluded from this study. Minor side-effects such as swelling and discomfort[14] have been reported with the use of acupressure bands. We used pulse oximetry[11] to demonstrate digital blood flow before the study. A single size elasticated acupressure band was used. To prevent minor complications, BMI >35 was used as an exclusion criterion. Patients with type 1 or type 2 diabetes mellitus are predisposed to delayed gastric emptying.[15] There is no evidence that gestational diabetes with good glycaemic control is associated with delayed gastric emptying and this group of mothers was considered for inclusion.

Patients were randomly allocated to one of two groups to receive either acupressure or control. Anaesthesia was administered by different anaesthetists using a standardized technique. All patients received ranitidine 150 mg p.o. 12 h and 2 h before the operation. Patients were given 0.3 M sodium citrate 30 ml orally in theatre. Five minutes before administration of spinal anaesthesia, acupressure bands (Sea band UK Ltd, Leicestershire, UK) were placed, in both groups, on the right forearm[17] by an anaesthetist not directly involved in patient care. This type of acupressure band has a flexible strap with a spherical plastic bead attached to it. In the acupressure group, wrist bands were placed with the plastic bead at the P6 point. The treatment point P6 ('Nei-Guan') is the number 6 meridian point in the pericardium channel; it is located on the anterior surface of the forearm between the tendons of flexor carpi radialis and palmaris longus, 2 'cun' (a cun is a Chinese measurement equal to the width of the interphalangeal joint of the thumb) from the distal wrist crease.[16] In the control group, a point on the dorsal side of the right forearm, 2 'cun' proximal to the distal wrist crease, was used for placebo stimulation. Bands were not visible to the assessing anaesthetist during operations, as patients' arms were covered with surgical drapes. Before assessment, 6 h after discharge to the ward, bands were removed by nursing staff.

After placement of standard monitors (automated arterial pressure, electrocardiogram and pulse oximetry), patients received oxygen by face mask 5 litres min^{-1}. One litre of lactated Ringer's solution was administered i.v., to which 30 mg of ephedrine hydrochloride was added to prevent maternal hypotension.[18] Thereafter, ephedrine-free lactated Ringer's solution was used. Subarachnoid puncture was performed with a 25 gauge Whitacre needle, with patients in the sitting position. A midline approach at the L2–3 or L3–4 interspace was used. Patients received 2.4 or 2.6 ml of 0.5% hyperbaric bupivicaine depending on their height (2.4 ml for those <152 cm and 2.6 ml for those >152 cm). Preservative-free morphine 0.2 mg was added to the bupivicaine. Patients were then placed in the supine position with left uterine displacement.

Non-invasive arterial pressure measurements were taken every 3 min until the patient left the theatre. A decrease in systolic arterial pressure (>20% from baseline or <100 mg Hg) was treated with i.v. ephedrine 3–6 mg increments. After delivery, oxytocin 10 IU i.v. and augmentin 1.2 g i.v. were administered. Estimated fluid deficit and maintenance were replaced with crystalloid solution. The criterion for supplemental analgesia was pain associated with surgical manipulation.[13] Fentanyl i.v. 1 $\mu g\ kg^{-1}$ was given as required.

Patients were questioned every 5 min concerning nausea. On a visual analogue scale of 0–10 a score of >2 was considered to indicate nausea. Anti-emetic (ondansetron 4 mg i.v. during operations[19] or cyclizine 50 mg i.m. 8 hourly after operations) was given if nausea or vomiting was intolerable.

The postoperative analgesia regimen was standardized. Rectal diclofenac 100 mg was given with prior consent at the end of the surgery. Morphine sulphate 0.1 mg kg^{-1} i.m. 4 hourly after 12 h was prescribed, as were diclofenac 100 mg 18 hourly p.r. and codeine 30 mg/paracetamol 500 mg 6 hourly. Chlorpheniramine 4 mg orally was available for symptomatic pruritis.

After 6 and 24 h, an anaesthetist blinded to the therapy noted whether nausea, retching or vomiting had occurred. The results were scored in a manner similar to that of Allen and colleagues[20] as (i) none, (ii) nausea or (iii) retching, vomiting or both. If a patient experienced both nausea and vomiting, they were listed as having vomited. Bands were removed 6 h after discharge to the ward, to avoid any possible local discomfort. Patients' charts were assessed at the end of 24 h for anti-emetic and analgesic requirements.

The physical characteristics of the two groups were assessed using the unpaired Student *t*-test. The groups were compared for overall nausea, retching and vomiting and then separately for nausea and vomiting during and after operations. Initially, Pearson's chi-squared test was used to investigate the association between nausea and vomiting in the acupressure and control groups. Then the odds ratio for acupressure and control of nausea and vomiting was estimated using a logistic regression model controlled for hypotension and age >33 yr during operations and in the 0–6 h and 6–24 h after operations. Non-parametric data were assessed using the rank sum sign test.

Results

Ninety-four patients participated in the study (47 in each group). Four patients were excluded because their BMI was >35 and two because of previous acupressure experience. The groups were comparable with respect to age, weight, height and bupivicaine dose (Table 1). The patients' obstetric and anaesthetic histories are shown in Table 2.

All patients received 1500–2000 ml crystalloid solution, and T4–5 block was achieved in all. The incidence of hypotension was similar in the two groups: 18 (38.3%) in the study group and 20 (42.5%) in the control group (P=0.67).

Eleven (23%) patients in the acupressure group and 25

Table 1 Patient characteristics and anaesthetic details (mean (SD or range)), using the unpaired *t*-test to calculate *P* values

	Acupressure ($n=47$)	**Control** ($n=47$)	***P* value**
Age (yr)	30 (18–38)	32 (19–40)	0.25
Weight (kg)	78 (12)	77 (11)	0.33
Height (cm)	163 (6)	160 (7)	0.27
Bupivicaine dose (ml)	2.51 (0.1)	2.55 (0.09)	0.15
Time wearing band on ward (h)	6.1 (6.0–6.3)	6.1 (6.0–6.3)	0.29

Table 2 Obstetric and anaesthetic history of patients (data are presented as number of patients and percentage of study group (SD))

	Acupressure ($n=47$)	**Control** ($n=47$)
Primiparous	30 (64%)	32 (68%)
Multiparous	17 (36%)	15 (32%)
Weeks' gestation	38.6 (1.4)	38.9 (1.4)
Previous Caesarian section	6 (13%)	8 (17%)
General anaesthesia	2 (4.3%)	1 (2%)
Regional anaesthesia	4 (8.5%)	7 (15%)

Table 3 Incidence (%) of nausea and vomiting, nausea only or vomiting, during and after operations

Period	**Acupressure** ($n=47$)	**Control** ($n=47$)	***P* value**
During operations	11 (23.4)	25 (53.2)	0.002
Nausea only	7 (14.9)	17 (36.2)	0.018
Vomiting	4 (8.5)	8 (17)	0.21
0–24 h after operations	17 (36.2)	31 (66)	0.003
Nausea only	4 (8.5)	6 (12.7)	0.50
Vomiting	13 (27.7)	25 (53.2)	0.011
0–6 h	16 (34)	29 (62)	0.007
6–24 h	3 (6)	10 (14)	0.03

Table 4 Opioid and anti-emetic requirements during and after operations; values are mean (range) (the rank sum sign test was used to assess statistical significance)

	Acupressure ($n=47$)	**Control** ($n=47$)	***P* value**
During operations			
Fentanyl µg	12.7 (0–100)	10.8 (0–100)	0.87
Ondansetron mg	0.08 (0–4)	0.5 (0–4)	0.002
0–24 h after operation			
Morphine mg	0.85 (0–10)	1.0 (0–10)	0.86
Cyclizine mg	13.0 (0–50)	25.0 (0–100)	0.002

Table 5 Odds ratio and 95% confidence interval of efficacy of acupressure in preventing nausea/vomiting (N/V) after adjustment for hypotension and age >33 yr; odds ratios were derived from a logistic regression model

Variable	**Odds ratio**	**95% CI**	***P* value**
N/V during Caesarian section	0.3	0.09–0.9	0.03
Hypotension	7.7	2.3–28.2	0.001
Age >33 yr	2.8	0.8–10.1	0.08
N/V 1–6 h	0.3	0.11–0.74	0.01
Hypotension	0.9	0.33–2.84	0.97
Age >33 yr	0.9	0.35–2.38	0.88
N/V 6–24 h	0.1	0.02–0.53	0.007
Hypotension	1.2	0.06–2.10	0.31
Age >33 yr	0.6	0.13–2.29	0.47

(53%) in the control group had nausea or vomiting during Caesarean section (P=0.002). Twenty-four hours after the operation 17 (36%) in the acupressure group and 31 (66%) in the control group had nausea or vomiting (P=0.003). There was a statistically significant reduction in nausea only (P=0.018) during operations in the acupressure group compared with control. After operations there was a statistically significant reduction in vomiting (P=0.011) in the acupressure group (Table 3).

Opioid requirements during and after operations were similar (Table 4). Twenty-three patients (50%) in the control group and 12 (25%) in the acupressure group required rescue anti-emetic in the study period (one or more dose) (P=0.01). There was a statistically significant difference in anti-emetic requirement during and after operations (Table 4).

If patients who received an anti-emetic intra-operatively were excluded, the protective effect of acupressure remained. The use of acupressure reduced the incidence of nausea and vomiting from 87% (35/40) to 50% (23/46) compared with placebo (95% CI 0.37–0.18, P=0.0002). With this analysis, the use of acupressure reduced anti-emetic requirement from 47% (19/40) to 26% (12/46) compared with placebo (95% CI 0.21–0.20, P=0.03).

The multiple variable analysis of data is presented in Table 5. Hypotension and age >33 yr was associated with increased risk of nausea or vomiting during Caesarean section but not at 6 and 24 h after operations. The odds ratio of nausea or vomiting during Caesarean section was about 30% in the acupressure group compared with control (adjusted for hypotension and age). This reduction was also evident during the 0–6 and 6–24 h periods.

Discussion

The mechanism of action of acupressure is still not known. Peripheral nerve stimulation must be an integral part of the mechanism as acupressure is not clinically effective if the nerve supply is disrupted.[21] Acupuncture has been shown to enhance gastric motility.[22] Treatment of vection-induced motion sickness by reducing gastric tachyarrhythmia has been demonstrated.[23]

Most published studies indicate the efficacy of acupressure or acupuncture at the P6 meridian. Belloumini and colleagues,[5] Fan and colleagues[6] and Dundee and colleagues[7] found this technique to be effective. In studies that have not had favourable results,[9 10] the technique was applied after the induction of anaesthesia. Acupuncture has been shown to effective by Al-Sadi and colleagues[24] after induction of anaesthesia but before opioid administration.[24]

Difficulties in acupuncture and acupressure research have been highlighted.[25–27] The question of what is an optimal control for acupuncture or acupressure has not been resolved. Acupuncture techniques raise expectations and involve a sensation; to facilitate blinding, control acupuncture should be indistinguishable from real acupuncture. It has been agreed that control acupuncture itself may have a specific effect.[28] This is particularly true with respect to analgesia research where location of the point is less important than in studies of nausea and vomiting studies.[29] Lewith and Vincent[30] have described sham acupuncture as a valid control in nausea and vomiting studies.

The incidence of nausea and vomiting in the control group during Caesarean section (53%) agrees with that reported elsewhere.[13] The incidence of nausea and vomiting in the control group in the first 24 h after operations (66%) differs from that of Abouleish and colleagues,[13] probably reflecting the small number of patients in their study. Our results do agree with results by Milner and colleagues,[4] with a higher incidence (66% *vs* 56%) resulting in part from our active questioning of patients' emetic symptoms and more frequent assessment.

We have demonstrated the effectiveness of P6 acupressure in reducing nausea and vomiting. The use of acupressure reduced the incidence of nausea and vomiting from 53% to 23% compared with placebo (95% CI 0.34–0.25; $P=0.002$) during operations and from 66% to 36% compared with placebo (95% CI 0.34–0.19; $P=0.003$) after operations. Significantly less anti-emetic was required by those in the treatment group ($P=0.01$).

Bands were removed 6 h after discharge to ward, but their effectiveness persisted in the 6–24 h interval, at a reduced level (odds ratio 0.1). There was a statistically significant reduction in the acupressure group, compared with controls, in nausea only ($P=0.018$) during operations and in vomiting ($P=0.011$) after operations. Nausea alone was the predominant symptom during operations and vomiting after operations.

From previous studies we know that nausea and vomiting follow a particular pattern in this setting, with nausea occurring early and vomiting later.[31] It is thought that this results from widespread dispersion of morphine throughout the subarachnoid and ventricular cerebrospinal fluid.

Routine use of anti-emetic drugs in patients during Caesarean section is not recommended by many because of adverse effects. Methoclopramide, which has been shown to have no deleterious affects on the neonate,[3] is most commonly used, but it is associated with extrapyramidal symptoms[32] and peripartum supraventricular tachycardias.[33] In our study, the only side effect of acupressure bands was some localized discomfort in a small number of women.

In conclusion, the non-pharmacological technique of acupressure at the P6 point is effective in preventing nausea and vomiting both during and after Caesarean section under spinal anaesthesia. Acupressure has no major side effects and is easy to apply and economical. Efficacy of acupressure before anaesthesia in combination with prophylactic anti-emetic drugs given after delivery is currently being examined.

References

1 Rowbotham DJ. Current management of postoperative nausea and vomiting. *Br J Anaesth* 1992; **69** (Suppl. 1): 46–59S

2 Korttila K. The study of postoperative nausea and vomiting. *Br J Anaesth* 1992; **69** (Suppl. 1). 20–23S

3 Lussos SA, Bader AM, Thornhill ML, Data S. The antiemetic efficacy and safety of prophylactic metoclopramide for elective Caesarean delivery during spinal anaesthesia. *Reg Anesth* 1992; **17**: 126–30

4 Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective Caesarean section. *Anaesthesia* 1996; **51**: 871–3

5 Belluomini J, Litt RC, Lee KA, Katz M. Acupressure for nausea and vomiting of pregnancy: a randomised, blinded study. *Obstet Gynecol* 1994; **84**: 245–8

6 Fan CF, Tanhui E, Joshi S, Trivedi S, Hong Y, Shevde K. Acupressure treatment for prevention of postoperative nausea and vomiting. *Anesth Analg* 1997; **84**: 821–5

7 Dundee JW, Ghaly RG, Fitzpatrick KTJ, Abram WP. Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *J R Soc Med* 1988; **82**: 268–71

8 Hu S, Chandler A, Stern RM. P6 acupressure reduces symptoms of vection-induced motion sickness. *Aviat Space Environ Med* 1995; **66**: 631–4

9 Yentis SM, Bissonnette B. P6 Acupuncture and postoperative vomiting after tonsillectomy in children. *Br J Anaesth* 1991; **67**: 779–80

10 Lewis IH, Pryn SJ, Reynolds PI, Pandit UA, Wilton NCT. Effect of P6 acupressure on postoperative vomiting in children undergoing outpatient strabismus correction. *Br J Anaesth* 1991; **67**: 73–8

11 Stein DJ, Birnbach DJ, Danzer BI, Kuroda MM, Grunebaum A, Thys DM. Acupressure versus intravenous metoclopramide to prevent nausea and vomiting during spinal anaesthesia for Cesarean section. *Anesth Analg* 1997; **84**: 342–5

12 Dahlgren G, Hulstrand C, Jakobson J, Norman M, Erickson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivicaine for cesarean section. *Anesth Analg* 1997; **85**: 1288–93

13 Abouleish E, Rawal N, Fallon K, Hernandez D. Combined intrathecal morphine and bupivicaine for cesarean section. *Anesth Analg* 1988; **67**: 370–4

14 Hyde E. Acupressure therapy for morning sickness: A controlled, clinical trial. *J Nurse Midwif* 1989; **34**: 171–8

15 Horowitz M, Wishart JM, Jones KL, Hebbard GS. Gastric emptying in diabetics: an overview. *Diabet Med* 1996; **13**: S16–22

16 Giovanni M. *The Foundations of Chinese Medicine.* Amersham: Churchill Livingstone, 1989; 435–6

17 Fitzpatrick KTJ, Dundee JW, Ghaly RG, Patterson CC. Is it necessary always to use the right forearm for acupuncture antiemesis? *Br J Anaesth* 1988; **61**: 117–18P.

18 Kang YG, Abouleish E, Curtis S. Prophylactic intravenous ephedrine infusion during spinal anaesthesia for Cesarean section. *Anesth Analg* 1982; **61**: 839–42

19 Pan YH, Moore CH. Introperative antiemetic efficacy of prophylactic ondansetron versus droperidol for Cesarean section patients under epidural anesthesia. *Anesth Analg* 1996; **83**: 982–6

20 Allen DL, Kitching AJ, Nagle C. P6 acupressure and nausea and vomiting after gynaecological surgery. *Anaesth Intensive Care* 1994; **22**: 691–3

21 Dundee JW, Ghaly G. Local anesthesia blocks the antiemetic action of P6 acupuncture. *Clin Pharmacol Ther* 1991; **50**: 78–80

22 Lin X, Liang J, Ren J, Mu F, Zhang M, Chen JDZ. Electrical stimulation of acupuncture points enhances gastric myoelectrical activity in humans. *Am J Gastroenterol* 1997; **92**: 1527–30

23 Hu S, Stern RM, Koch KL. Electrical acustimulation relieves vection-induced motion sickness. *Gastroenterology* 1992; **102**: 1854–8

24 Al-Sadi M, Newman B, Julious S. Acupuncture in the prevention of postoperative nausea and vomiting. *Anaesthesia* 1997; **52**: 658–61

25 Ernst E, White AR. A review of problems in clinical acupuncture research *Am J Chin Med* 1997; **25**: 3–11

26 Harden RN. The pitfalls of clinical acupuncture research: can east satisfy west? *Arthritis Care Res* 1994; **7**· 115–17

27 Vickers AJ. Can acupuncture have specific effects on health? A systematic review of acupuncture antiemesis trials. *J R Soc Med* 1996; **89**: 303–11

28 Richardson PH, Vincent CA. Acupuncture for the treatment of pain: a review of evaluative research. *Pain* 1986; **24**: 15–40

29 Vincent C, Lewith G. Placebo controls for acupuncture studies. *J R Soc Med* 1995; **88**: 199–202

30 Lewith GT, Vincent CA. On the evaluation of the clinical effects of acupuncture: a problem reassessed and a framework for future research. *J Altern Complement Med* 1996; **2**: 79–90

31 Bromage PR, Camporesi EM, Durant PAC, Neilson CH. Nonrespiratory side effects of epidural morphine. *Anesth Analg* 1982; **61**: 490–5

32 Cadwell C, Rains G, McKiterick K. An unusual reaction to preoperative metoclopramide. *Anesthesiology* 1987; **67**: 854–5

33 Bevacqua BK. Supraventricular tachycardia associated with postpartum metoclopramide administration. *Anesthesiology* 1987; **68**· 124–5

British Journal of Anaesthesia 84 (4): 468–75 (2000)

BJA

LABORATORY INVESTIGATION

Continuous measurements of microcirculatory blood flow in gastrointestinal organs during acute haemorrhage

V. Krejci[1], L. Hiltebrand[1], A. Banic[2], D. Erni[2], A. M. Wheatley[3] and G. H. Sigurdsson[1]*

[1]Department of Anaesthesia and Intensive Care, [2]Department of Plastic and Reconstructive Surgery and [3]Department of Visceral and Transplantation Surgery, Inselspital, University Hospital of Berne, CH-3010 Berne, Switzerland

**Corresponding author*

Hypoperfusion of splanchnic organs is an important contributor to the development of multiple organ failure after major surgery and trauma. During general anaesthesia and surgery we compared changes in systemic haemodynamics and regional blood flow with changes in the distribution of microcirculatory flow (MBF) in multiple splanchnic organs in pigs exposed to acute haemorrhage. Seven pigs (25 kg) were bled to a mean arterial pressure of 40 mm Hg; 180 min later the shed blood was retransfused. MBF was measured in the intestinal mucosa (stomach, jejunum, colon), pancreas, liver and kidney using a six-channel laser Doppler flowmeter. Cardiac output was measured by thermodilution and superior mesenteric artery flow by ultrasonic flowmetry. During haemorrhage, MBF in the gastric and colon mucosa and flow in the liver and kidney decreased to a similar extent to regional and systemic flows (30–50%). In contrast, MBF in the jejunal mucosa remained virtually unchanged and flow in the pancreas decreased significantly more than systemic and regional flows (60%, $P<0.05$). We conclude that: (1) changes in the distribution of MBF in the gastrointestinal tract during acute haemorrhage are heterogeneous and cannot be predicted from changes in systemic or regional haemodynamics; (2) MBF in the jejunal mucosa did not decrease during haemorrhage, indicating that autoregulation of blood flow in the mucosa remained intact during shock; and (3) MBF in the pancreas decreased significantly more than systemic and regional flows during shock, suggesting that the pancreas is particularly vulnerable to haemorrhage.

Br J Anaesth 2000; **84**: 468–75

Keywords: blood, flow, microcirculatory; blood, loss; measurement techniques, blood flow; pig

Accepted for publication: November 11, 1999

Multiple organ failure syndrome remains a major cause of morbidity and mortality in critically ill patients.[1] [2] It is believed that hypoperfusion of splanchnic organs,[3–5] resulting from trauma, haemorrhage or disease, is an important contributor to the development of multiple organ failure (MOF) and death.[6] [7] Although blood flow in the gastrointestinal tract has received increased attention from scientists in recent years, the difficult access to the gut in humans has hampered clinically relevant studies.[8] Therefore, most controlled studies have been performed in animal models. However, very few have studied the distribution of flow within different regions and different organs of the gastrointestinal tract during acute haemorrhage.[9] Furthermore, many of the studies on blood flow in the gastrointestinal tract in shock have been performed in rodents,[10] which are known to differ from larger animals (such as pigs) and humans in the microvascular architecture in the intestinal wall.[11]

During acute haemorrhage, the splanchnic circulation is greatly affected by local and systemic regulatory mechanisms, which may cause immediate and sustained hypoperfusion of the gastrointestinal tract.[12] Although measurements of superior mesenteric artery blood flow or analysis of lactate in portal blood may give some information about splanchnic perfusion, very little is known about dynamic changes within different organs of the gastrointestinal tract during haemorrhage. With the recent availability of multichannel laser Doppler flowmetry (LDF) systems, continuous and simultaneous measurements of microcirculatory blood flow (MBF) from several organs has become possible.[13]

The objectives of the present study were to measure

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

changes in dynamic distribution of MBF in multiple gastrointestinal organs (gastric, jejunal and colon mucosa, pancreas, liver) and the kidney and to compare it with systemic haemodynamics and regional blood flow during acute haemorrhage in anaesthetized pigs.

Materials and methods

This study was performed according to NIH guidelines for the use of experimental animals and the protocol was approved by the Animal Ethics Committee of Canton Berne. Twelve pigs (24–30 kg) were given ketamine 10 mg kg^{-1} i.m. followed 10 min later by metomidate 5 mg kg^{-1} and azaperone 2 mg kg^{-1} i.v. for tracheal intubation. Anaesthesia was maintained with 0.5–0.6% halothane (end-tidal concentrations) in nitrous oxide–oxygen (ratio 2:1) together with an i.v. infusion of fentanyl 15 μg kg^{-1} h^{-1} and pancuronium 0.3 mg kg^{-1} h^{-1}. Inhaled and exhaled concentrations of nitrous oxide and halothane were monitored continuously with a multi-gas analyser (Hellige SMU 611; Hellige, Freiburg, Germany). The animals were ventilated with a volume-controlled ventilator with a positive end-expiratory pressure (PEEP = 4–5 cm H_2O) (Tiberius 19; Drägerwerk, Lübeck, Germany). Tidal volume was kept at 10 ml kg^{-1} and the respiratory rate adjusted (13–18 min^{-1}) to maintain Pa_{CO_2} between 4.5 and 5.5 kPa.

During surgery the animals received Ringer's lactate 15–20 ml kg^{-1} h^{-1}, which kept central venous and pulmonary capillary wedge pressures constant. After surgery the rate of infusion of Ringer's lactate was reduced to 7 ml kg^{-1} h^{-1}. The animals' body temperature was kept at 38.2±0.25°C using two heating blankets.

A gastric tube (Tonometrics Inc., Worcester, MA, USA) was inserted orally into the stomach, and the balloon was prepared according to the manufacturer's recommendations to completely evacuate excess air and filled with 2.5 ml of 0.9% NaCl. Correct position of the tonometry tube was verified after laparotomy. Abdominal aortic and pulmonary artery (Arrow, Reading, PA, USA) catheters were inserted via the femoral artery and veins and a large-bore central venous catheter was inserted via the internal jugular vein.

After midline laparotomy, the spleen was removed to prevent autotransfusion as splenic contraction can contribute up to 25% of the red cell volume in pigs,[14] and a urinary bladder catheter was inserted. Small antimesenteric incisions were made on stomach, small intestine and colon, to allow small-angled LDF probes (Oxford Optronix, Oxford, UK) to be sutured on to the mucosal surface. Six microsutures per probe were used to prevent motion artefacts from respiration and bowel movement. The incisions on the intestinal wall were closed with sutures. Additional probes were sutured on the surface of the left kidney and the pancreas. One probe was attached to the surface of the left liver lobe using six special blunt needles.

The signals from the LDF device were observed continuously on a computer monitor during probe installation; the position of the probes could be corrected immediately if there was inadequate signal or if motion artefacts occurred. Once the experiment was started, manipulation was avoided to minimize the possibility of probe displacement.

An ultrasonic transit time flow-probe (Transonic Systems Inc., Ithaca, NY, USA) of appropriate size (1.5–3 mm) was placed around the superior mesenteric artery. A catheter for blood sampling was inserted in the mesenteric vein. The abdomen was then flushed with warm saline (38°C) and the laparotomy was closed with sutures and clamps before the experiment was started.

Experimental protocol

After completion of surgery the animals were allowed to stabilize for 30–60 min before baseline measurements were performed. The conditions were considered stable when all measurement values remained within 10% for 30 min. Five animals served as controls. Controls were treated as the test animals, except that they were not subject to haemorrhage/resuscitation. Seven animals underwent haemorrhagic shock and subsequent retransfusion of shed blood. Following the baseline measurements, blood was withdrawn from the central venous catheter into a heparinized bag until the mean arterial pressure reached 40 mm Hg. After 180 min of hypovolaemic shock, the shed blood was retransfused over 30 min and the animals were observed for another 90 min.

Gas measurements (end-tidal carbon dioxide, end-tidal halothane and inspired oxygen concentrations), systemic haemodynamics (heart rate, mean arterial blood pressure, central venous pressure, pulmonary artery pressure, pulmonary artery wedge pressure), superior mesenteric artery flow, MBF in the liver, pancreas, kidney and mucosa of the stomach, jejunum and colon were measured continuously throughout the experiment. Cardiac index measurements and blood samples were taken at 30, 60, 120 and 180 min after haemorrhage and at 210, 240, 170 and 300 min (30, 60, 90 and 120 min after retransfusion, respectively). At the end of the experiment the animals were killed with an overdose of i.v. potassium.

Haemodynamic monitoring

Mean arterial blood pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP) and pulmonary capillary wedge pressures (PCWP) were recorded with quartz pressure transducers (129A; Hewlett-Packard, Andover, MA, USA) and displayed continuously on a multimodular monitor (Hellige SMU 611) and recorder (Hellige SMR 821). ECG was monitored continuously, and heart rate was estimated from the ECG. Cardiac index was measured by a thermodilution technique (mean of three measurements, Hellige SMU 611 cardiac output module). Central venous blood temperature was recorded from a thermistor in the pulmonary artery catheter. Blood samples for haemoglobin and haematocrit analysis were withdrawn from the aortic artery catheter.

Table 1 Systemic haemodynamics in animals exposed to haemorrhagic shock MAP, mean arterial blood pressure, CVP, central venous pressure; PAP, pulmonary artery pressure, PWP, pulmonary artery wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance $^*P<0.05$ compared with baseline

	Baseline mean (SEM)	**Change as per cent of baseline, mean (SEM)**						
		Time after haemorrhage				**Time after retransfusion**		
		30 min	**60 min**	**120 min**	**180 min**	**30 min**	**60 min**	**120 min**
Cardiac index	204 (18) ml kg^{-1} min^{-1}	53 (6)*	55 (5)*	54 (5)*	55 (5)*	84 (8)	95 (8)	97 (8)
Heart rate	90 6 (4.8) beats min^{-1}	125 (14)	156 (12)*	167 (8)*	187 (9)*	134 (5)*	139 (10)*	145 (9)*
MAP	95 4 (5 2) mm Hg	43 (3)*	43 (3)*	43 (3)*	42 (3)*	75 (8)	74 (7)*	72 (7)*
CVP	7.71 (0.92) mm Hg	44 (6)*	47 (12)*	49 (11)*	54 (9)*	124 (21)	101 (15)	89 (21)
PAP	21 3 (1 3) mm Hg	68 (4)*	74 (6)*	80 (9)	86 (7)	135 (7)*	111 (7)	110 (4)
PWP	7.71 (0 84) mm Hg	39 (5)*	47 (8)*	48 (9)*	46 (8)*	118 (13)	94 (11)	91 (10)
SVR	1644 (169) dyn s^{-1} cm^{-5}	85 (5)	81 (6)*	82 (7)*	77 (7)*	86 (9)	77 (7)	74 (6)*
PVR	253 (28) dyn s^{-1} cm^{-5}	173 (19)*	176 (19)*	192 (28)*	209 (27)*	181 (20)*	132 (9)*	129 (8)

Respiratory monitoring

Expired minute volume ventilation, tidal volume, respiratory rate, PEEP, peak and end inspiratory pressures, inspired and end-tidal carbon dioxide concentration ($ETCO_2$), and inspired and expired oxygen concentrations were monitored continuously throughout the study. Respiratory compliance (chest wall and lung; C_T) was calculated as expiratory tidal volume (TV) divided by end-inspiratory airway pressure minus PEEP (P_{aw}). Both values were recorded simultaneously from the ventilator. Blood samples for arterial blood gas analysis were withdrawn from the aortic artery catheter and analysed immediately (temperature corrected) in a blood gas analyser (ABL 620; Radiometer, Copenhagen, Denmark).

Gastric tonometry

The tonometer balloon was filled with 2.5 ml of 0.9% NaCl. After 30 min of equilibration, 1 ml of NaCl (dead space) was discarded and PCO_2 was measured in the remaining 1.5 ml in a blood gas analyser (ABL 620, Radiometer) and corrected with a time-dependent correction factor provided by the manufacturer. Intramucosal pH was calculated from arterial bicarbonate and corrected PCO_2 using the Henderson–Hasselbach equation.

Oxygen delivery and oxygen consumption

Global and splanchnic oxygen delivery and consumption were calculated from blood flow and from arterial, mixed venous and mesenteric venous blood gases using standard formulae.

Ultrasonic transit time flowmetry

Blood flow in the mesenteric artery was continuously measured throughout the experiment with ultrasonic transit time flowmetry (TTF) using an HT 206 flowmeter (Transonic Systems Inc.).

Laser Doppler flowmetry

MBF was measured continuously with a six-channel laser Doppler flowmeter system (Oxford Array, Oxford Optronix). The suturable miniature surface probes used (SP 300, Oxford Optronix) were designed to measure MBF to a depth of 0.7 mm into the tissue. The multichannel laser Doppler unit and probes were calibrated by the manufacturer using a motility standard (suspension of latex particles) and an appropriate calibration key for a specific set of laser Doppler probes was attached to the unit. The LDF signals and the TTF signal were exported via analogue outputs and acquired on-line via a multichannel interface (Mac Paq MP 100; Biopac Systems Inc., Goleta, CA, USA) with acquisition/analysis software (Acqknowledge 3.0; Biopac Systems Inc.) to a portable computer.

A detailed description of the theory of LDF operation and practical details of LDF measurements have been described before.[15 16] Briefly, low energy laser light from a solid-state diode laser operating at 780±10 nm is guided to the measurement site via an optical fibre. Two identical adjacent fibres receive back-scattered light from the tissue which is then transmitted to independent photodetectors. This back-scattered portion consists of light scattered from the static tissue matrix which has not been Doppler shifted and a spectrally broadened component resulting from interactions with moving blood cells. Optical mixing of these components at the photodetector surface produces an electrical signal containing all the Doppler frequency shift information. Further processing within the frequency range of 20–12 kHz produces an output voltage which varies linearly with the product of mean blood cell velocity and concentration. The product of mean blood cell velocity and concentration is correctly referred to as the blood cell flux, but since flow rate may also be defined as volume flux then, as long as the number of red cells within a volume of blood remains constant, the blood cell flux will be proportional to the volume flux or flow of blood.

Laser Doppler devices are not calibrated to measure absolute blood flow, as different tissues have different optical properties. Instead, they indicate MBF in arbitrary perfusion units. Baseline values are very variable, so results are usually expressed as changes relative to baseline.[16 17] The quality of the LDF signal was controlled on-line by visualization on a computer screen, so that motion artefacts and noise due to inadequate probe attachment could be

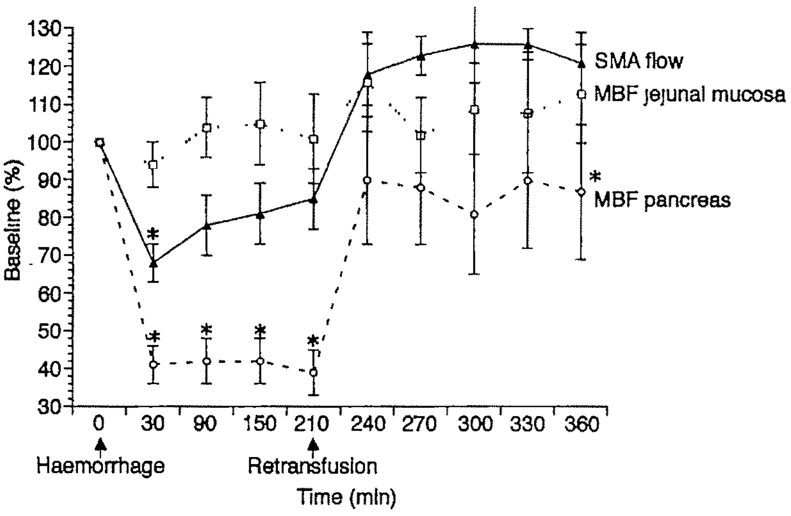


Fig 1 Changes (mean (SEM)) in the superior mesenteric artery flow (SMA flow) and in microcirculatory blood flow (MBF) in the jejunal mucosa and in the pancreas after haemorrhage and after retransfusion of shed blood. Baseline values were: SMA flow, 47 (12) ml min^{-1}; MBF of jejunal mucosa, 259 (9) perfusion units (PU), MBF of pancreas, 753 (257) PU. The SMA flow decreased after blood loss to a similar extent to cardiac index and recovered after retransfusion. MBF in the pancreas decreased more after haemorrhage and failed to recover fully after retransfusion. In contrast, MBF in the jejunal mucosa was not affected by blood loss or by retransfusion. *$P<0.05$ compared with baseline

immediately detected and corrected before the measurements started.

Statistical analysis and data presentation

Data are presented as mean (SEM). Nonparametric Wilcoxon rank sum test was used to describe changes relative to baseline. For correlation of measurements nonparametric Spearman correlation was used. $P<0.05$ was considered statistically significant. A computer program for statistical analysis (InStat 2.03 for Macintosh; GraphPad Software, San Diego, CA, USA) was used for all calculations.

Results

Systemic and regional haemodynamics

The main results are presented in Table 1. After haemorrhage, filling pressures (PCWP and CVP), MAP, cardiac index and SVR decreased, while PVR increased ($P<0.05$). Retransfusion of shed blood restored filling pressures and cardiac index. MAP also increased but it remained 28% below baseline ($P<0.05$). SVR also remained low (26% below baseline) but PVR decreased after retransfusion. At the end of haemorrhage, SMA flow was 32% below baseline ($P<0.05$), but after 3 h of shock it was 15% below baseline. After retransfusion of the shed blood, SMA flow increased to 21% above baseline (Fig. 1, $P<0.05$). The changes in SMA flow correlated well with changes in cardiac index ($r=0.91$, $P<0.05$)

MBF in the intestinal mucosa

After haemorrhage the MBF in the gastric and colon mucosa decreased by 28% ($P<0.05$) and 23% respectively. After retransfusion of shed blood, MBF increased to 16% above baseline in the gastric mucosa and returned to baseline in the colon mucosa (Table 2). MBF in the jejunal mucosa was virtually unaffected by haemorrhage and retransfusion (Fig. 1)

MBF in the pancreas, liver and kidney

After haemorrhage, MBF in the liver decreased by 36% ($P<0.05$) and in the kidney by 40% ($P<0.05$). After retransfusion of shed blood, MBF in the liver returned to baseline in both organs (Table 2). MBF in the pancreas decreased by 61% during haemorrhage and remained 13% below baseline after retransfusion (Fig. 1).

Gastric tonometry

Gastric intramucosal pH (pH$_i$) was 7.27 (0.02) at baseline and decreased to 7.15 (0.03) after 180 min of haemorrhagic shock ($P<0.05$). After retransfusion of shed blood, pH$_i$ increased slightly but did not reach baseline values (7.20 (0.03); $P<0.05$). The difference between arterial P_{CO_2} and the P_{CO_2} measured by gastric tonometry was 1.73 (0.39) kPa at baseline and increased to 2.63 (0.54) kPa ($P<0.05$) after haemorrhage. After retransfusion it was 1.72 (0.56) kPa (Table 3).

Oxygen transport and oxygen consumption

Systemic oxygen delivery decreased by 60% and splanchnic oxygen delivery by 40% after haemorrhage. Systemic oxygen extraction increased from 31% to 75% and splanchnic oxygen extraction from 36% to 65%. After retransfusion these parameters returned to baseline values except for global oxygen extraction which decreased, but remained 30% above baseline. Oxygen consumption remained unchanged throughout the experiment both globally and in the splanchnic region (Table 4).

Table 2 Microcirculatory blood flow (MBF) measured with laser Doppler flowmetry in animals exposed to haemorrhagic shock Baseline data are presented as mean (SEM) perfusion units (PU) Changes after haemorrhage and retransfusion are expressed as mean (SEM) per cent of the baseline $^*P<0.05$ compared with baseline

	Baseline MBF (PU) mean (SEM)	**Change in MBF, mean (SEM) per cent of baseline**						
		Time after haemorrhage				**Time after retransfusion**		
		30 min	**60 min**	**120 min**	**180 min**	**30 min**	**60 min**	**120 min**
Gastric mucosa	224 (22)	65 (10)*	79 (12)	73 (10)*	72 (11)*	107 (18)	121 (19)	116 (21)
Colon mucosa	243 (22)	84 (9)	83 (11)	82 (10)	77 (11)	123 (17)	103 (12)	105 (8)
Liver	924 (268)	71 (8)*	70 (11)	67 (12)	64 (14)	85 (11)	106 (6)	101 (7)
Kidney	640 (115)	72 (9)*	60 (9)*	62 (11)*	60 (11)*	84 (13)	95 (22)	107 (21)

Table 3 Arterial blood gases and gastric tonometry data. Hb=haemoglobin, Sa_{O_2}, arterial oxygen saturation; Pa_{O_2}, arterial oxgen partial pressure, Pa_{CO_2}, arterial carbon dioxide partial pressure, pH_a, arterial pH, BE, arterial base excess, pH_i, gastric intramucosal pH, Pi_{CO_2} gastric intramucosal carbon dioxide partial pressure measured by gastric tonometry. All values are presented as mean (SEM). $^*P<0.05$ compared with baseline

	Baseline	**Time after haemorrhage**				**Time after retransfusion**		
		30 min	**60 min**	**120 min**	**180 min**	**30 min**	**60 min**	**120 min**
Haemoglobin (g litre^{-1})	97 (5)	83 (5)*	74 (6)*	74 (5)*	70 (5)*	90 (5)*	90 (3)	87 (3)
Sa_{O_2} (%)	94.6 (0.1)	94.8 (0.1)*	94.8 (0.2)	94.9 (0.1)*	94.9 (0.1)*	94.5 (0.2)	94.3 (0.3)	94.4 (0.3)
Pa_{O_2} (kPa)	18.0 (0.6)	17.0 (0.8)	18.4 (1.2)	17.4 (0.9)	18.2 (1.4)	17.2 (0.9)	16.1 (1.0)	15.8 (1.1)
Pa_{CO_2} (kPa)	5.0 (0.1)	5.0 (0.2)	5.6 (0.3)	5.2 (0.2)	5.2 (0.1)	5.2 (0.1)	5.1 (0.1)	5.1 (0.2)
pH_a	7.45 (0.01)	7.43 (0.02)	7.39 (0.04)	7.39 (0.02)	7.38 (0.02)*	7.39 (0.03)	7.41 (0.01)	7.42 (0.02)
BE (mmol litre^{-1})	1.7 (0.9)	0.8 (0.5)	−0.6 (1.3)	−1.4 (1.4)*	−1.8 (1.5)*	−1.4 (1.5)*	−0.2 (1.2)	−0.1 (1.0)*
pH_i	7.23 (0.02)	7.20 (0.03)*	7.16 (0.03)*	7.17 (0.02)*	7.15 (0.03)*	7.17 (0.02)	7.20 (0.03)*	7.20 (0.03)*
Pi_{CO_2}–Pa_{CO_2} (kPa)	1.73 (0.39)	2.14 (0.50)	2.56 (0.59)*	2.47 (0.26)	2.63 (0.54)*	1.75 (0.72)	1.68 (0.52)	1.72 (0.56)

Table 4 Oxygen delivery and consumption in animals exposed to haemorrhagic shock After haemorrhage, systemic oxygen delivery (Do_2 systemic) decreased in parallel with flow (cardiac index). Total body oxygen extraction (ER systemic) and splanchnic oxygen extraction (ER splanchnic) increased during shock, keeping systemic (Vo_2 systemic) and splanchnic (Vo_2 splanchnic) oxygen consumption unchanged. Baseline values are presented as mean (SEM) Changes after haemorrhage and retransfusion are expressed as mean (SEM) per cent of the baseline except for ER values which are presented as absolute values $^*P<0.05$ compared with baseline

	Baseline	**Change in parameter as per cent of baseline**						
		Time after haemorrhage				**Time after retransfusion**		
		30 min	**60 min**	**120 min**	**180 min**	**30 min**	**60 min**	**120 min**
Do_2								
systemic	26 (3) ml kg^{-1} min^{-1}	45 (5)*	42 (4)*	42 (4)*	41 (5)*	78 (8)	89 (10)	88 (8)
splanchnic	0.24 (0.05) ml kg^{-1} min^{-1}	58 (4)*	60 (5)*	62 (6)*	62 (7)*	110 (9)	118 (12)	109 (6)
Vo_2								
systemic	7.9 (0.5) ml kg^{-1} min^{-1}	88 (5)*	95 (5)*	92 (5)*	93 (5)*	97 (3)*	102 (5)	108 (5)
splanchnic	0.09 (0.02) ml kg^{-1} min^{-1}	99 (8)*	107 (10)*	115 (12)	119 (19)	94 (13)	86 (7)	95 (10)
ER								
systemic	31 (2) %	65 (1)*	73 (1)*	71 (1)*	73 (1)*	47 (3)	44 (4)	46 (5)
splanchnic	36 (3) %	65 (2)*	68 (3)*	69 (3)*	67 (4)*	40 (5)	35 (3)*	40 (5)

Control group

There were no significant changes in any of the parameters measured in the control group. Some of the main parameters are summarized in Table 5.

Discussion

It is generally recognized that sufficient splanchnic blood flow is vital for positive outcome of patients exposed to major surgery or trauma,[6 7] yet treatment of patients in circulatory shock is still frequently guided by systemic haemodynamic parameters alone. This is a result of the difficulty of access to the gastrointestinal tract. Direct measurements of regional or local splanchnic blood flow are invasive, time consuming and require special skills and instruments that are not readily available at the bedside. In order to evaluate the dynamic relationship between systemic, regional and local splanchnic blood flows during the development of haemorrhagic shock in anaesthetized subjects we, therefore, used an animal model. We chose the pig for this study because of its anatomical and physiological similarity to humans with respect to the cardiovascular system and the digestive tract.[18] The laser Doppler technique, which was used to monitor MBF in this study, has been validated for measuring flow in many organs including the intestinal mucosa,[19] the liver,[15] the pancreas[20] and the

Table 5 Systemic haemodynamics, regional and microcirculatory blood flow (MBF) in control animals, not exposed to haemorrhagic shock MAP, mean arterial blood pressure, PU, perfusion units, SMA flow, superior mesenteric artery flow. Baseline data are presented as mean (SEM) (n=5). *P<0.05 compared with the baseline [a] Except for haemoglobin concentration, which is presented in g litre^{-1}, mean (SEM)

	Baseline	**Change, mean (SEM) per cent of baseline**[a]						
		30 min	**90 min**	**150 min**	**210 min**	**240 min**	**300 min**	**360 min**
Haemoglobin	95 (4) g litre^{-1}	95 (4)	99 (4)	101 (4)	100 (4)	101 (3)	102 (4)	101 (2)
MAP	87 (6) mm Hg	100 (2)	99 (4)	97 (3)	97 (4)	96 (3)	100 (3)	97 (4)
Cardiac index	191 (21) ml kg^{-1} min^{-1}	92 (3)	87 (3)	90 (3)	95 (6)	94 (7)	93 (11)	93 (10)
SMA flow	40 (11) ml min^{-1}	103 (5)	109 (8)	118 (13)	136 (12)	128 (8)	124 (20)	128 (21)
MBF								
Gastric mucosa	229 (18) PU	98 (6)	94 (5)	103 (7)	101 (8)	104 (8)	115 (14)	107 (9)
Jejunal mucosa	256 (14) PU	101 (3)	102 (4)	107 (8)	114 (10)	120 (7)	109 (13)	117 (15)
Colon mucosa	365 (55) PU	96 (3)	87 (6)	90 (5)	91 (6)	91 (6)	92 (6)	98 (12)
Pancreas	841 (203) PU	100 (8)	94 (9)	90 (11)	95 (14)	96 (17)	105 (20)	95 (17)
Liver	859 (261) PU	95 (9)	93 (12)	99 (11)	109 (13)	106 (17)	117 (21)	102 (14)
Kidney	626 (48) PU	100 (10)	101 (11)	106 (13)	105 (8)	100 (7)	104 (9)	115 (15)

kidney.[21] The technique is based on detecting moving erythrocytes in the microvasculature, and is therefore sensitive to motion artefacts such as respiratory movements, gastrointestinal motility and shivering. By using small, lightweight, custom-made, flexible probes sutured (with microsutures) to the tissue under observation it was possible to prevent such artefacts.

In awake subjects the normal acute response to blood loss includes increased peripheral vascular resistance due in large part to vasoconstriction in splanchnic organs.[22] Indeed splanchnic hypoperfusion may persist for several hours after systemic haemodynamics have been restored.[12] General anaesthesia is known to influence central haemodynamics and regional blood flow and it depresses the normal sympathetic and humoral response to hypovolaemia.[23] In the anaesthetized animals used in our study, systemic vascular resistance fell after haemorrhage and mesenteric blood flow was better maintained than cardiac output. The slight increase of superior mesenteric artery flow during haemorrhagic shock might be explained by decreasing splanchnic vascular resistance over time.[24] Furthermore, after retransfusion of shed blood, mesenteric blood flow rose to above baseline while the recovery of cardiac output was less marked. Thus, the acute response to blood loss may differ between anaesthetized and conscious subjects.

The decrease in MBF in the gastric and colon mucosa (approximately 30%) was similar to the decrease observed in regional blood flow (Table 2). This reduction in gastric mucosal blood flow was accompanied by gastric mucosal acidosis manifested by an increased difference between arterial and mucosal $P\text{CO}_2$ ($Pi_{\text{CO}_2} - Pa_{\text{CO}_2}$; Table 3). After retransfusion of shed blood, gastric mucosal blood flow and the $Pi_{\text{CO}_2} - Pa_{\text{CO}_2}$ gap returned to baseline. There was a positive correlation between the change in MBF in the gastric mucosa and the $Pi_{\text{CO}_2} - Pa_{\text{CO}_2}$ gap (r=0.36, P<0.01). This finding suggests that the laser Doppler flowmeter did indeed measure changes in nutritive blood flow in the gastric mucosa during haemorrhagic shock.

In contrast to MBF in the mucosa of the stomach and colon, flow in the jejunal mucosa was unaffected by haemorrhage despite the significant decrease in systemic and regional flows. This suggests that autoregulation of blood flow in the jejunal mucosa remains intact during acute haemorrhage in anaesthetized pigs It is possible that, under these circumstances, blood flow is directed away from the muscularis layer towards the mucosa.[25]

It has been suggested that redistribution of blood flow during haemorrhagic shock from tissues with low oxygen demand towards tissues with a high oxygen demand is an important mechanism for maintaining oxygen consumption independent from supply. Increased vascular tone mediated by neurohumoral factors in tissues with a low oxygen demand seems to play an important role in this mechanism.[26] After electric stimulation of splanchnic nerves a decreased blood flow in the intestinal wall is followed by an 'autoregulatory escape' of microcirculatory blood in the small intestinal mucosa, particularly in the villus region[27] but to a much lesser extent in the muscularis. It has also been shown that exposure of the small intestinal mucosa to nutrients leads to mucosal hyperaemia due to autoregulation of blood flow to the absorptive site[28] and, when blood flow to the intestine is reduced, this autoregulation seems to occur at the expense of the intestinal segments not exposed to nutrients.[29] Furthermore, vasoactive drugs influence the distribution of blood flow in the gut. Both isoproterenol and adenosine[30] cause a significant increase in total blood flow to the intestinal wall. However, isoproterenol favours blood flow to the mucosa while adenosine favours flow to the mucularis layer. Both vasodilators depress oxygen uptake in the intestine.

Thus, under certain conditions, redistribution of blood flow from the muscularis layer to the mucosa does occur; however, to our knowledge, intact autoregulation of blood flow in the intestinal mucosa remains to be demonstrated in haemorrhagic shock. Thus, it appears that local control mechanisms of blood flow in the small intestine favour flow to the mucosa at the cost of the muscularis during hypovolaemia.[27] It is possible that this autoregulation is facilitated or even controlled by high oxygen demand[31] in the mucosa together with very low oxygen tension in the intestinal villi.

During blood loss, the decrease in MBF in the pancreas was greater (–60%) than the changes seen in systemic (–45%) and regional (–30%) flows. Arterial blood pressure also decreased by 60% as compared with baseline, suggesting the absence of autoregulation of blood flow in the pancreas during haemorrhage. After retransfusion of shed blood the pancreas blood flow did not return to baseline values in contrast to the other organs studied. No other organ showed such a profound decrease in local blood flow during haemorrhage or such persistent hypoperfusion after retransfusion of shed blood. This finding is in accordance with studies on anaesthetized dogs exposed to haemorrhagic shock[32] where total blood flow to the pancreas decreased proportionally more than blood flow in the superior mesenteric artery. In a study by Bor and colleagues,[33] pancreatic blood flow, measured using the ^{33}Xe washout technique, decreased to the same extent as systemic blood pressure. Thus, MBF in the pancreas appears to be more susceptible to hypovolaemia than other splanchnic organs. It has also been shown that morphological and functional damage occurs in the pancreas after haemorrhage.[34] Thus, it is likely that pancreatic hypoperfusion may contribute to the development of remote organ dysfunction in critically ill or injured patients.[35]

Conclusions

Changes in the distribution of microcirculatory (local) blood flow in the gastrointestinal tract are heterogeneous during haemorrhagic shock and cannot be predicted from systemic or regional blood flow in anaesthetized pigs. Splanchnic regional blood flow and MBF in the gastric and colon mucosa decrease to a similar extent as systemic flow during haemorrhage and hypoperfusion does not persist after retransfusion of shed blood. It appears that autoregulation of blood flow in the jejunal mucosa is intact in anaesthetized pigs during haemorrhagic shock. MBF in the pancreas appears to decrease more than in any other splanchnic organ during acute haemorrhage.

References

1 Sigurdsson GH. Prevention of sepsis and multiple organ failure in critically ill patients. *Acta Anaesthesiol Scand* 1995; (Suppl. 105) **39**: 23–30

2 Jabs C, Sigurdsson G, Neglen P. Plasma levels of high energy compounds compared with severity of illness (APACHE II score) in critically ill ICU patients. *Surgery* 1998; **124**: 65–72

3 Arden WA, Yacko MA, Jay M, Beihn RM, Derbin M, Gross DR *et al.* Scintigraphic evaluation of bacterial translocation during hemorrhagic shock. *J Surg Res* 1993; **54**: 102–6

4 Sigurdsson GH. Is translocation of bacteria and endotoxin from the gastrointestinal tract a source of sepsis in the critically ill? *Acta Anaesthesiol Scand* 1995; **39** (Suppl. 105): 11–19

5 Turnbull RG, Talbot JA, Hamilton SM. Hemodynamic changes and gut barrier function in sequential hemorrhagic and endotoxic shock. *J Trauma* 1995; **38**: 705–12

6 Landow L, Andersen LW. Splanchnic ischemia and its role in multiple organ failure. *Acta Anaesthesiol Scand* 1994; **38**: 626–39

7 Sigurdsson GH, Christenson JT, El-Rakshy MB, Sadek S. Intestinal platelet sequestration after traumatic and septic shock. An early sign of sepsis and multiple organ failure in critically ill patients? *Crit Care Med* 1992; **20**: 458–67

8 Uusaro A, Ruokonen E, Takala J. Estimation of splanchnic blood flow by the Fick principle in man and problems in the use of indocyanine green. *Cardiovasc Res* 1995; **30**: 106–12

9 Carter EA, Tompkins RG, Yarmush ML, Walker WA, Burke JF. Redistribution of blood flow after thermal injury and hemorrhagic shock. *J Appl Physiol* 1988; **65**: 1782–8

10 Wang P, Hauptman JG, Chaudry IH. Hemorrhage produces depression in microvascular blood flow which persists despite fluid resuscitation. *Circ Shock* 1990; **32**: 307–18

11 Chou CC. Gastrointestinal circulation and motor function. In: Shultz S, Wood J, Rauner B, eds. *Handbook of Physiology—The Gastrointestinal System*, Vol. 1. New York: Oxford University Press, 1989; 1475–517

12 Edouard AR, Degremont AC, Duranteau J, Pussard E, Berdeaux A, Samii K. Heterogeneous regional vascular responses to simulated transient hypovolemia in man. *Intensive Care Med* 1994; **20**: 414–20

13 Erni D, Banic A, Wheatley AM, Sigurdsson GH. Haemorrhage during anaesthesia and surgery: continuous measurement of microcirculatory blood flow in the kidney, liver, skin and skeletal muscle. *Eur J Anaesthesiol* 1995; **12**. 423–9

14 Hannon JP, Bossone CA, Rodkey WG. Splenic red cell sequestration and blood volume measurements in conscious pigs. *Am J Physiol* 1985; **248**: R293–301

15 Almond NE, Wheatley AM. Measurement of hepatic perfusion in rats by laser Doppler flowmetry. *Am J Physiol* 1992; **262**: G203–9

16 Kuznetsova L, Tomasek N, Sigurdsson G, Banic A, Wheatley A. Estimation of muscle blood flow and resistance by laser Doppler flowmetry during changes in vascular tone. *Am J Physiol* 1998; **274**: H1248–54

17 Banic A, Krejci V, Erni D, Wheatley A, Sigurdsson G. Effects of sodium nitroprusside and phenylephrine on blood flow in free musculocutaneous flaps during general anesthesia. *Anesthesiology* 1999; **90**: 147–55

18 Dodds WJ. The pig model for biomedical research. *Fed Proc* 1982; **41**: 247–56

19 Kvietys PR, Shepherd AP, Granger DN. Laser-Doppler, H2 clearance, and microsphere estimates of mucosal blood flow. *Am J Physiol* 1985; **249**: G221–7

20 Norstein J, Lien B, Hall C, Kvernebo K, Morkrid L, Soreide O, *et al.* Measurement of pancreas parenchyma perfusion by laser-Doppler flowmetry. *Transplant Proc* 1990; **22**: 607–8

21 Smits GJ, Roman RJ, Lombard JH. Evaluation of laser-Doppler flowmetry as a measure of tissue blood flow. *J Appl Physiol* 1986; **61**: 666–72

22 Schadt JC, Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am J Physiol* 1991; **260**: H305–18

23 Dalibon N, Schlumberger S, Saada M, Fischler M, Riou B. Haemodynamic assessment of hypovolaemia under general anaesthesia in pigs submitted to graded haemorrhage and retransfusion. *Br J Anaesth* 1999; **82**: 97–103

24 Gallavan R, Parks D, Jacobson E. Pathophysiology of gastrointestinal circulation. In: Shultz S, Wood J, Rauner B, eds. *Handbook of Physiology–The Gastrointestinal System*, Vol. 1. New York: Oxford University Press; 1989; 1713–32

25 Connolly HV, Maginniss LA, Schumacker PT. Transit time heterogeneity in canine small intestine: significance for oxygen transport. *J Clin Invest* 1997; **99**: 228–38

26 Samsel RW, Schumacker PT. Systemic hemorrhage augments local O2 extraction in canine intestine. *J Appl Physiol* 1994; **77**: 2291–8

27 Shepherd AP, Riedel GL. Intramural distribution of intestinal blood flow during sympathetic stimulation. *Am J Physiol* 1988; **255**: H1091–5

28 Granger HJ, Norris CP. Intrinsic regulation of intestinal oxygenation in the anesthetized dog. *Am J Physiol* 1980; **238**: H836–43

29 Larson MV, Ahlquist DA, Karlstrom L, Sarr MG. Intraluminal measurement of enteric mucosal perfusion: relationship to superior mesenteric artery flow during basal and postprandial states in the dog *Surgery* 1994; **115**: 118–26

30 Shepherd AP, Riedel GL, Maxwell LC, Kiel JW. Selective vasodilators redistribute intestinal blood flow and depress oxygen uptake *Am J Physiol* 1984; **247**: G377–84

31 Granger DN, Kvietys PR, Korthuis RJ, Premen AJ. Microcirculation of the intestinal mucosa. In: Shultz S, Wood J, Rauner B, eds. *Handbook of Physiology—The Gastrointestinal System*, Vol. 1. New York: Oxford University Press, 1989; 1405–74

32 Robert JH, Toledano AE, Toth LS, Premus G, Dreiling DA. Hypovolemic shock, pancreatic blood flow, and pancreatitis *Int J Pancreatol* 1988; **3**: 283–92

33 Bor NM, Alvur M, Ercan MT, Oner G, Bekdik CF. Pancreatic blood flow in hemorrhagic shock. *Pflugers Arch* 1980; **386** 277–80

34 Barzilai A, Medina JA, Toth L, Dreiling DA. The effect of hypovolemic shock on pancreatic secretion *Int J Pancreatol* 1986; **1**: 373–9

35 Gober I. The effect of hypovolaemic shock on the pancreas (author's translation). *Wien Klin Wochenschr* Suppl. 1975; **39**: 1–11

British Journal of Anaesthesia **84** (4): 476–88 (2000)

BJA

REVIEW ARTICLE

P2X receptors in sensory neurones

G. Burnstock

Autonomic Neuroscience Institute, Royal Free and University College Medical School, Rowland Hill Street, London NW3 2PF, UK

P2X receptors are a family of ligand-gated ion channels responsive to ATP. Seven subtypes have been identified which form homomultimeric or heteromultimeric pores. $P2X_3$ receptors are selectively expressed predominantly on small-diameter nociceptive sensory neurones in the dorsal root, trigeminal and nodose ganglia, particularly the non-peptidergic subpopulations labelled with the lectin IB4. $P2X_{2/3}$ labelling is also present in inner lamina II of the spinal cord and in sensory nerve projections to skin and viscera, but few receptors are present in skeletal muscle. $P2X_3$ receptors are down-regulated after peripheral nerve injury and their expression can be regulated by glial cell-derived neurotrophic factor. P2X receptor activation of sensory neurones has been demonstrated in *in vivo* pain models, including the rat hindpaw and knee-joint preparations, as well as in inflammatory models. $P2X_4$ and/or $P2X_6$ receptors in the CNS also seem to be involved in pain pathways. Non-nociceptive P2 receptors on sensory nerves are present in muscle and on sensory endings in the heart and lung that initiate reflex activity involving vagal afferent and efferent nerve fibres. The sources of ATP involved in nociception and non-nociceptive sensory nerve stimulation are discussed as well as a novel hypothesis about purinergic mechanosensory transduction.

Br J Anaesth 2000; **84**: 476–88

Keywords: nerve, neurotransmitters; pain

There have been various reports over the years about the actions of ATP on sensory nerves.[9 10 15 22 45 84] However, it was only recently that direct evidence for P2 receptors of various subtypes on sensory neurones was obtained after the cloning and characterization of extracellular receptors for ATP from sensory nerves;[39 88] subsequent studies have confirmed and extended this finding.[8 29 38 42 43 61 77 105 126 132 139] In this article, the evidence for nociceptive and mechanosensitive P2X and P2Y receptors on sensory neurones, and for P2X receptors involved in sensory pathways in cardiorespiratory reflexes and in the CNS, is reviewed. The origin of ATP acting on sensory neurones and the interactions of P2 sensory receptors with other agents will be discussed.

Early reports of extracellular actions of ATP

The first report describing the potent actions of adenine compounds was published in 1929 by Drury and Szent-Györgyi[52] and the first hint that ATP might be a neurotransmitter appeared three decades later when ATP was shown to be released during antidromic stimulation of sensory nerves supplying the rabbit ear artery.[71] In the early 1960s, the existence of autonomic nerves supplying the gastrointestinal tract and urinary bladder that were neither adrenergic nor cholinergic was proposed.[18 32 33 98] In the years that followed, strenuous efforts were made to identify the transmitter in non-adrenergic, non-cholinergic nerves supplying the gut and the urinary bladder. Perhaps surprisingly, the substance that most satisfied the criteria accepted at that time for establishing a transmitter[54] was ATP,[34] and the word 'purinergic' was coined and purinergic transmission proposed.[19]

Implicit in the concept of purinergic transmission was the existence of postjunctional receptors for ATP, although there was considerable confusion in the literature about the variable effects of adenosine nucleotides and nucleosides on a wide variety of tissues.[20] However, a step forward was taken in 1978 when, from a detailed analysis of the literature and some preliminary experiments, it was proposed[21] that purinoceptors could be subdivided into P1 (adenosine) receptors, which were mediated by adenylate cyclase and competitively antagonized by low concentrations of methylxanthines, and P2 receptors, which were activated preferentially by ATP and ADP. Two of the most important implications of this purinoceptor subdivision were: (1) the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

importance of establishing if, in a particular situation, ATP was acting directly on P2 receptors or via P1 receptors after ectoenzymatic breakdown to adenosine;[103] and (2) during purinergic transmission, whereas ATP released from the nerve terminals acted on postjunctional P2 receptors, adenosine arising from extracellular breakdown of ATP acts largely via P1 receptors on the nerve terminals to modulate release of transmitters.[47] Prejunctional modulation via P1 receptors operates both as a negative feedback system in autoregulation of purinergic transmission and to modulate the release of noradrenaline (NA), acetylcholine (ACh) and other neurotransmitters released with ATP.[26]

P2 receptor subclassification

In 1985, Burnstock and Kennedy[36] proposed the first subdivision of P2 receptors into: P2X purinoceptors, which mediate vasoconstriction and contraction of visceral smooth muscle with α,β-methylene ATP as a potent agonist; and P2Y purinoceptors, which mediate vasodilatation and relaxation of the smooth muscle of the gut with 2-methylthio ATP as a particularly potent agonist. Soon afterwards, two further P2 purinoceptors were tentatively proposed:[63] a P2T purinoceptor, which is ADP-selective and involved in platelet aggregation, and a P2Z purinoceptor, which appears to be activated by ATP^{4-} and is prominent in macrophages, lymphocytes and mast cells. Another important landmark, after the seminal studies of Furchgott and Zawadski,[59] was the recognition that ATP acts on endothelial cells to mediate vasodilatation via release of endothelium relaxing factor (EDRF).[48] This important discovery challenges the early hypothesis of Berne[7] that adenosine is the local regulator of blood flow after hypoxia in heart and other vascular beds—it now seems likely that reactive hyperaemia results largely from ATP released from endothelial cells during hypoxia acting on P2Y receptors to release EDRF (nitric oxide), resulting in vasodilatation; adenosine, produced after the breakdown of ATP, is likely to contribute to the later component of vasodilatation by direct action on P1 receptors on vascular smooth muscle.[25]

Knowledge of the structure and properties of P2 receptors has lagged behind information about receptors for most other neurotransmitters, although advances have been made recently. The general progress of information about purinoceptors has been: structure–activity relationships, pharmacology, quantification of receptor expression, ligand binding and autoradiographic localization, transduction mechanisms involving second messenger systems and ion channels, and finally the molecular biology of the receptors with cloning and sequencing. Since the earlier subdivisions of the P2 purinoceptor into P2X, P2Y, P2T and P2Z mentioned above, several further subclasses were proposed, including P2U purinoceptors where ATP and UTP are equipotent[110] and a P2D purinoceptor, selective for diadenosine polyphosphates.[114] It was clearly shown that P2X purinoceptors involved ligand-gated cation channels,[6] while P2Y receptors involved G protein activation.[53] More recently, it has been suggested that some P2Y receptors act via G_i proteins to inhibit adenylate cyclase[69] and that there may be pyrimidine nucleotide-selective G protein-linked receptors.[41, 106]

The first P2 receptors to be cloned were G protein-coupled receptors; a P2Y receptor, $P2Y_1$, was isolated from chick brain[141] and a P2U purinoceptor (later designated $P2Y_2$) from neuroblastoma cells.[95] A year later, two ligand-gated ion channel ATP receptors were reported—one ($P2X_1$) from vas deferens[134] and another ($P2X_2$) from rat phaeochromocytoma PC12 cells.[17]

In the paper from the IUPHAR subcommittee concerned with the nomenclature of P2 purinoceptors,[58] it was emphasized that the current purinoceptor subclassification, with so many letters of the alphabet being somewhat randomly added as new receptor subtypes were discovered, was unsatisfactory. The Committee supported, in principle, a new system of classification proposed by Abbracchio and Burnstock.[1] In this proposal, it was suggested that P2 receptors should be placed in two major families: a P2X family, consisting of ligand-gated cation channels, and a P2Y family, consisting of G protein-coupled receptors. The P2Z purinoceptor, which opens non-selective pores, has recently been cloned and incorporated into the P2X receptor family as $P2X_7$.[125] This classification brought ATP into line with most other neurotransmitters, such as ACh, γ-amino butyric acid (GABA), glutamate and 5-hydroxytryptamine, where ligand-gated and G protein-mediated receptor subclassification has already been established.[28] Seven P2X family and eight P2Y family subtypes have been identified to date.[29, 30, 37, 109]

P2X receptor family

For the P2X receptor subtypes the proteins deduced from cDNA sequences have 379 ($P2X_6$) to 472 ($P2X_7$) amino acid residues and share 36–48% identity with each other. They are characterized by two transmembrane (TM) domains with a large extracellular loop where 10 cysteines are preserved; both N- and C-terminals are intracellular. Northern blots and *in situ* hybridization show a widespread distribution of mRNA with $P2X_1$ expressed predominantly in smooth muscle, $P2X_4$ and $P2X_6$ most heavily expressed in brain, $P2X_3$ found only in sensory neurones and $P2X_7$ dominant in cells of the immune system.[12, 40, 125] $P2X_1$–$P2X_4$ subtypes readily form homomultimeric channels when expressed in oocytes or in transfected mammalian cell lines; the number of subunits per channel, although not yet established, is believed to be three or four.[38, 107, 108] It is also becoming clear that many of the naturally occurring P2X receptors are heteromultimers of the P2X subtypes.[81, 86, 137]

P2Y receptor family

The eight P2Y purinoceptor subtypes respond more slowly to agonists than the P2X purinoceptor and achieve their effect through intracellular second messenger systems.

As for other known G protein-coupled receptors, the molecule is characterized by seven TM domains with short extracellular N- and intracellular C-terminals.[3] The receptor consists of a 308–377 amino acid, with a mass of 41–53 kDa after glycosylation; TM3 displays a high degree of conserved amino acid residues within the P2Y purinoceptor family.[13, 135] Northern blots and *in situ* hybridization show a wide distribution of most P2Y receptor subtypes.[4, 69] The possibility that P2Y$_4$, together with other subtypes, should be considered as a subfamily of pyrimidinoceptors within the P2Y purinoceptor family has been raised.[41]

The identification of selective agonists and antagonists for the different P2X and P2Y receptor subtypes is still awaited. Meanwhile, in general, 2-methylthio ATP is most active at native P2Y receptors, while α,β-methylene ATP is more active at most native P2X receptors, although there are clear exceptions and the reported potencies of some agonists is complicated by their breakdown by ecto-nucleotidases.[35, 77] Some receptor subtypes are selectively activated by UTP and others are not, while some exhibit desensitization and others do not.[108] P2 receptor antagonists in current use, including suramin, pyridoxal-phosphate-6-axophenyl-2′,4′-disulphonic acid (PPADS), and Reactive blue 2, do not appear to be selective for different recombinant receptor subtypes, but have been used selectively in isolated preparations.[28] There are few reports of the use of antagonists *in vivo*.

P2 receptors on sensory neurones

Nociceptive P2X receptors

The amino acid sequence of a novel P2X purinoceptor subtype (P2X$_3$) has been described.[39, 88] This receptor is present in a subset of dorsal root ganglion (DRG) sensory neurones that express peripherin, a cytoskeletal protein associated with small-diameter sensory neurones.[39] A high proportion of these small-diameter neurones are nociceptive. These results raise the possibility that ATP might play an important role in nociceptor activation (Fig. 1).

A molecular mechanism for the pain-inducing actions of ATP has been suggested by studies of rat sensory neurones in culture. Electrophysiological analysis has shown that between 40% and 96% of DRG sensory neurones in culture respond to ATP by increasing intracellular free calcium concentrations ([Ca^{2+}]$_i$) or by depolarizing.[5, 15, 115, 116] P2X$_{1-6}$ mRNA transcripts are expressed in sensory neurones of the dorsal root, nodose and trigeminal ganglia.[108] However, only one subtype, P2X$_3$, is expressed selectively in cell populations enriched in nociceptors, as judged by *in situ* hybridization analysis with markers for small-diameter neurones. This demonstrates that other P2X purinoceptors probably account for the depolarizing actions of ATP on large-diameter neurones. The level of expression of mRNA detected by *in situ* hybridization and Northern blots suggests that P2X$_3$ is present in greater amounts than other P2X subunits, such as P2X$_2$, in small-diameter sensory neurones.

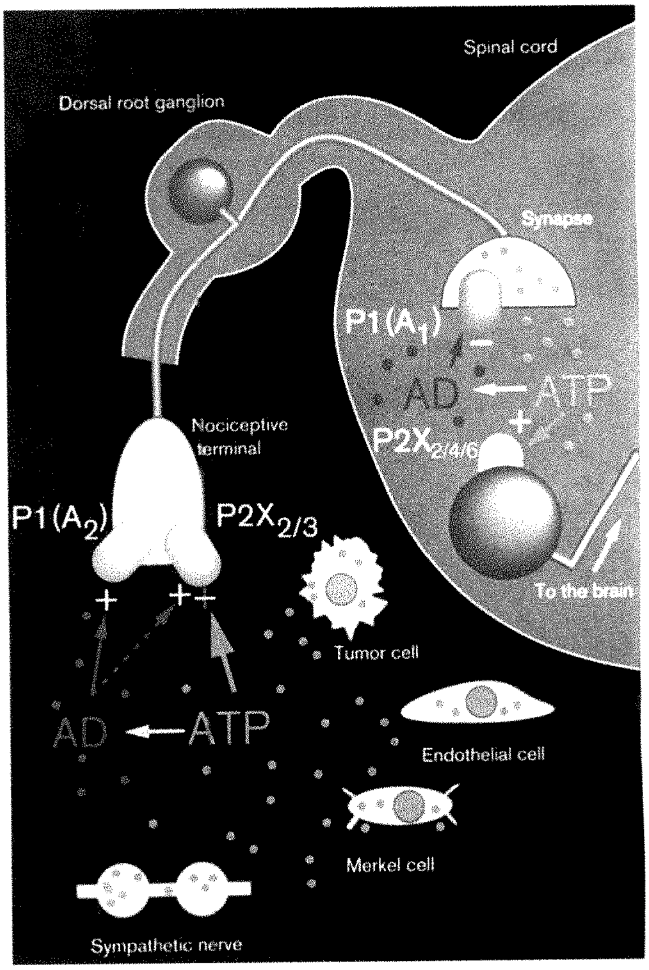


Fig 1 Hypothetical schematic of the roles of purine nucleotides and nucleosides in pain pathways. P2X$_3$ has been identified as the principal P2X receptor present at sensory nerve terminals in the periphery. P2X$_3$ receptors are also found in sensory ganglia where they sometimes form heteromultimers with P2X$_2$ receptors. Other known P2X receptor subtypes are also expressed at low levels in DRG. Although less potent than ATP, adenosine (AD) also appears to act on sensory terminals, probably directly via P1 (A$_2$) receptors; however, it may also act (broken line) to potentiate P2X$_{2/3}$ activation. At synapses in sensory pathways in the CNS, ATP appears to act postsynaptically via P2X$_2$, P2X$_4$ or P2X$_6$ receptor subtypes, or two or more of these subtypes, and after breakdown to adenosine, it acts as a prejunctional inhibitor of transmission via P1 (A$_1$) receptors. Sources of ATP acting on P2X$_{2/3}$ sensory terminals include sympathetic nerves and endothelial, Merkel and tumour cells. White dots, molecules of ATP; grey dots, molecules of adenosine. (From Burnstock and Wood, 1996.[38])

An electrophysiological analysis of the properties of the expressed P2X$_3$ channel showed many similarities with currents in rat sensory neurones in culture.[116] Thus the channel rapidly desensitized, and was activated by ATP congeners with the same rank order of potency as that described for sensory neurones in culture (at low concentrations, 2-methylthio ATP >> ATP > α,β-methylene ATP > γ-thioATP > CTP > ADP >> UTP ≈ β,γ-methylene ATP > GTP).[39] In addition, the channel is blocked by suramin, a general antagonist of P2X purinoceptors (with the exception of P2X$_4$ and P2X$_6$). However, it is not clear

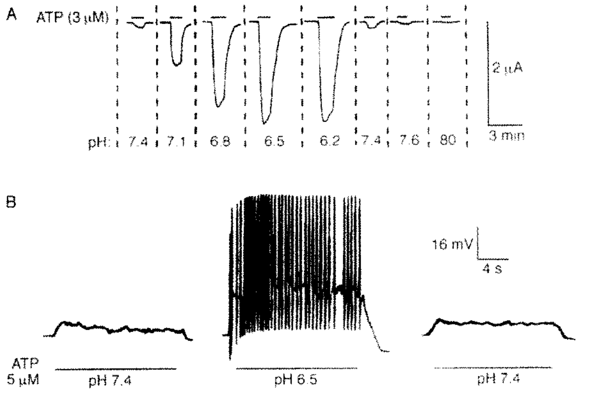


Fig 2 Effect of extracellular pH on sensitivity to ATP. (A) In *Xenopus* oocytes expressing the P2X$_2$ receptor, the activity of successive superfusion of ATP (3 μM) was increased by acidifying the bathing solution from pH 7.4 to 6.2, but decreased by alkanization from pH 7.4 to 8.0 (inward current, V_H = −30 mV). (B) Acid pH increases membrane depolarization and action potential firing elicited by ATP. Records are voltage responses to ATP (5 μM) at pH 7.4 and 6.5 in a single neurone from rat nodose ganglion with a resting membrane potential of −54 mV in current-clamp configuration. Traces are sequential (from left to right). Action potential amplitude was attenuated by the frequency-response of the pen recorder (100 Hz). ((A) From King and colleagues, 1996;[82] (B) from Li and colleagues, 1996.[89])

if P2X$_3$ exists as a homomultimer or a heteromultimer with P2X$_2$ in sensory neurones *in vivo*. In a recent study of rat nodose ganglion neurones using 2′,3′-*O*-trinitrophenyl ATP (TNP-ATP) as a selective P2X antagonist, it was concluded that some neurones used homomeric P2X$_2$ receptors, whereas others used heteromeric P2X$_{2/3}$ receptors.[129 136 137] Evidence has been presented that the capsaicin-sensitive, small DRG neurones of the rat express mainly the homomultimeric P2X$_3$ subunit, while the capsaicin-insensitive, medium-sized neurones express the heteromultimeric P2X$_{2/3}$ receptor.[133]

Indirect evidence for heteromultimeric channels in sensory neurones has been provided by co-expression of P2X subunits in *Xenopus* oocytes. Some nodose ganglion neurones desensitize slowly in response to α,β-methylene ATP, but P2X$_3$ shows a rapid desensitization in oocytes. However, co-expression of P2X$_2$ and P2X$_3$ produces a channel that has a slowly desensitizing response.[88] This confirms that the heteromultimeric channels are able to form, and may account for, some slowly desensitizing responses in subsets of sensory neurones.

It seems likely, as discussed above, that P2X$_3$ receptors form heteromultimeric combinations with P2X$_2$ receptors. Thus, while P2X$_3$ receptors are not sensitive to pH, recombinant P2X$_2$ receptors are strongly pH-sensitive[82 91 142] (Fig. 2), suggesting that sensitivity to nociceptive P2 receptors is enhanced in inflammatory conditions with slow acidosis. Acid pH has also been shown to augment the excitatory actions of ATP on dissociated mammalian sensory neurones.[89] In contrast, physiological concentrations of extracellular Mg^{2+} inhibit ATP-activated current in rat nodose ganglion cells.[90] A more recent study of dissociated neurones from 1- to 4-day old rat DRG showed that the relative actions of various ATP analogues and, in particular, the very low activity of β,γ-methylene-L-ATP confirmed the presence of P2X$_3$ receptors.[115] Synergistic interactions between ATP and other known nociceptive agents on sensory terminals in the periphery have been proposed.[64 72 73 142] The ability of P2X$_3$ receptors to be activated by repetitive concentrations of ATP without desensitization is greatly enhanced by the presence of Ca^{2+}.[44] This enhancement occurs if Ca^{2+} is applied early or late in the interval between ATP applications and this 'memory' for elevated Ca^{2+} persists for at least 4 min.

Immunohistochemical studies of P2X$_3$ receptors on sensory ganglia at both light microscope[11 16 138–140 143] and electron microscope level[94] show that:

(1) P2X$_3$ receptors are predominantly located in the non-peptidergic subpopulation of small nociceptive neurones that label with the lectin IB4;[16 138–140 143]
(2) in trigeminal ganglia, P2X$_3$ receptor immunoreactivity occurs in both small and large nerve cell bodies and their processes;
(3) P2X$_3$ receptors are expressed in approximately equal numbers of sensory neurones projecting to the skin and viscera (Fig. 3), but in very few of those innervating skeletal muscle;[16]
(4) the central projections of P2X$_5$-labelled nerves in the DRG are located in inner lamina II of the dorsal horn of the spinal cord;[16 94 140]
(5) for the labelled nerve profiles in lamina II, P2X$_3$ receptors are located largely in terminals that have the ultrastructural characteristics of sensory afferent terminals (Fig. 4), suggesting that ATP is released on to primary afferent terminals, thereby modulating sensory input coming from the periphery;[94]
(6) in the nucleus solitarius, P2X$_3$ receptor-positive boutons synapse on dendrites and cell bodies and have complex synaptic relationship with other axon terminals and dendrites;[94]
(7) the peripheral projections of nociceptive neurones in the skin, tongue and tooth pulp are immunopositive for P2X$_3$ receptors;[11]
(8) after sciatic nerve axotomy, P2X$_3$ receptor expression decreased by more than 50% in L4/5 DRG (Fig. 5). Glial cell-derived neurotrophic factor (GDNF), delivered intrathecally, completely reversed axotomy-induced down-regulation of the P2X$_3$ receptor (Fig. 6).[16] In contrast, the P2X$_3$ receptor was transiently up-regulated and anterogradely transported in trigeminal primary sensory nerves after nerve injury.[56]

In vivo pain models. In vivo studies of the functional consequences of P2X receptor activation of peripheral neurones in animal models are beginning to appear. Behavioural indices of acute nociception were monitored in the conscious rat after subplantar injection of ATP and α,β-methylene ATP into the hindpaw.[8] Signs of overt nocicep-

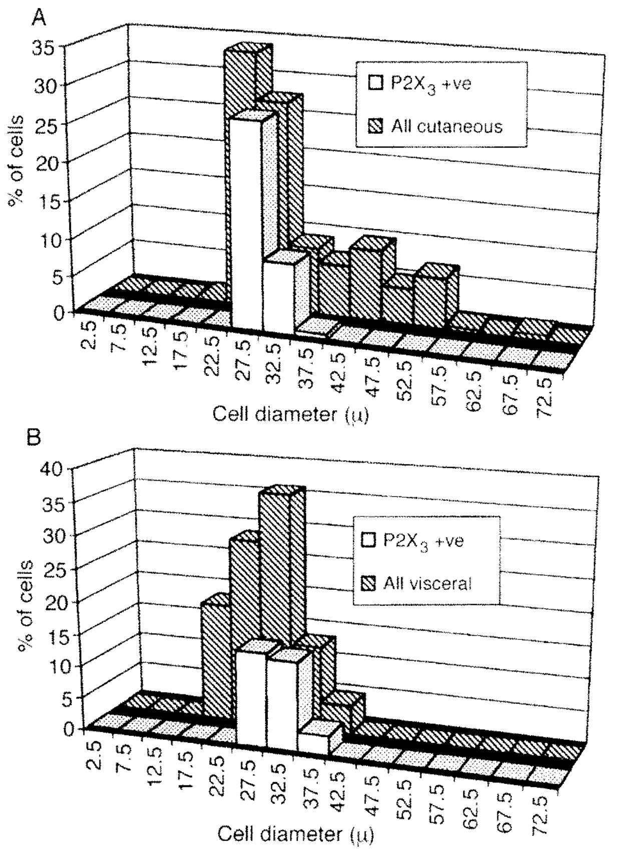


Fig 3 Size distribution of cutaneous (A) and visceral (B) afferents (hatched bars), labelled by fluoro-gold application to the saphenous and pelvic nerves, respectively. The size distribution of fluoro-gold-labelled cells immunoreactive for the $P2X_3$ receptor is shown by the open bars. (From Bradbury and colleagues, 1998.[16])

tion, namely hindpaw lifting and licking, were apparent after injection of α,β-methylene ATP; these effects were dose-related and inhibited by selective desensitization of the $P2X_3$ receptor. The results of another study using this model suggested that endogenous ATP in inflamed skin is more likely to reach a concentration capable of exciting nociceptors than in normal skin.[67] ATP and α,β-methylene ATP were applied to the peripheral terminals of primary afferent articular nociceptors in rat knee joints and neural activity was recorded from the medial articular nerve in rats anaesthetized with pentobarbitone.[50] Rapid, short-lasting excitation of a subpopulation of C and Aδ nociceptive afferents was evoked, which was antagonized by PPADS.

Experiments have also been carried out using the formalin rat-paw model, which has two distinct components: an initial phase which reflects a direct sensory nerve activation, and a later phase which may reflect an inflammatory component.[130] The P2 antagonists, suramin, Evans blue, Trypan blue and Reactive blue 2, produced antinociception in this model when applied intrathecally.[51] Sawynok and Reid[120] concluded that their results provided evidence in support of a P2X receptor-mediated augmentation of the pain signal and that the delayed time-course of the effects suggested that it may occur in concert with other mediators that are recruited by the inflammatory process. In another study, using the formalin and writhing tests in adult male albino mice, systemically administered ATP and ADP, which are rapidly degraded to adenosine, caused a *reduction* in the number of writhes and the time of licking the formalin-injected paw.[102] However, P1, but not P2 antagonists reversed these reactions, so it was concluded that the antinociceptive effects of adenosine nucleotides were mediated by adenosine. An early study using the 'hot-plate' test claimed that ATP produced analgesia.[62]

Mechanosensitive P2 receptors

In a study of rat sensory neurones in culture, nociceptive (tooth-pulp afferent) and non-nociceptive (muscle stretch receptors) sensory neurones were compared (Fig. 7).[43] Low concentrations of ATP evoked action potentials and large inward currents in both types of neurone. Nociceptors had currents that were similar to those of heterologously expressed channels containing $P2X_3$ subunits and had $P2X_3$ immunoreactivity in their cell bodies and sensory endings. Stretch receptors had currents that differ from those of $P2X_3$ channels and had no $P2X_3$ immunoreactivity.

A single cRNA derived from sensory neurones, which renders *Xenopus* oocytes mechanosensitive, was found to encode a $P2Y_1$ receptor.[105] $P2Y_1$ mRNA is concentrated in large-fibre DRG neurones, in contrast to $P2X_{2/3}$ mRNA, which is found in small-fibre sensory neurones and produces less mechanosensitivity in oocytes. The frequency of touch-induced action potentials from frog sensory nerve fibres was increased by the presence of P2 receptor agonists at the peripheral nerve endings and was decreased by antagonists. The authors postulate that release of ATP into the extracellular space activates peripheral $P2Y_1$ receptors participating in the generation of sensory action potentials by light touch. In another recent study, ATP has been shown to induce Ca^{2+} release from IP_3-sensitive Ca^{2+} stores exclusively in large DRG neurones.[126] The ATP-triggered increase in the intracellular concentration of Ca^{2+} was not mimicked by adenosine and was blocked by suramin (Fig. 8) and the authors concluded that large (proprioceptive) DRG neurones express metabotropic P2Y receptors. In a later publication,[127] this group concluded that Ca^{2+}-impermeable ionotropic P2X receptors are present in subpopulations of mouse DRG neurones with large somatas (30–45 μm diameter) as well as metabotropic P2Y receptors.

Cardiorespiratory reflexes

Many years ago, functional studies by Emmelin and Feldberg[55] showed that intravenously administered ATP slowed the cat heart via reflex actions involving vagal afferent and efferent nerve fibres. ATP also acts on canine pulmonary vagal C-fibre nerve terminals[112] and on sensory terminals in the heart setting up vagal reflexes in both dog and humans.[113]

More recently, P2X receptors associated with vagal afferent nerves have been shown to evoke a Bezold–Jarisch

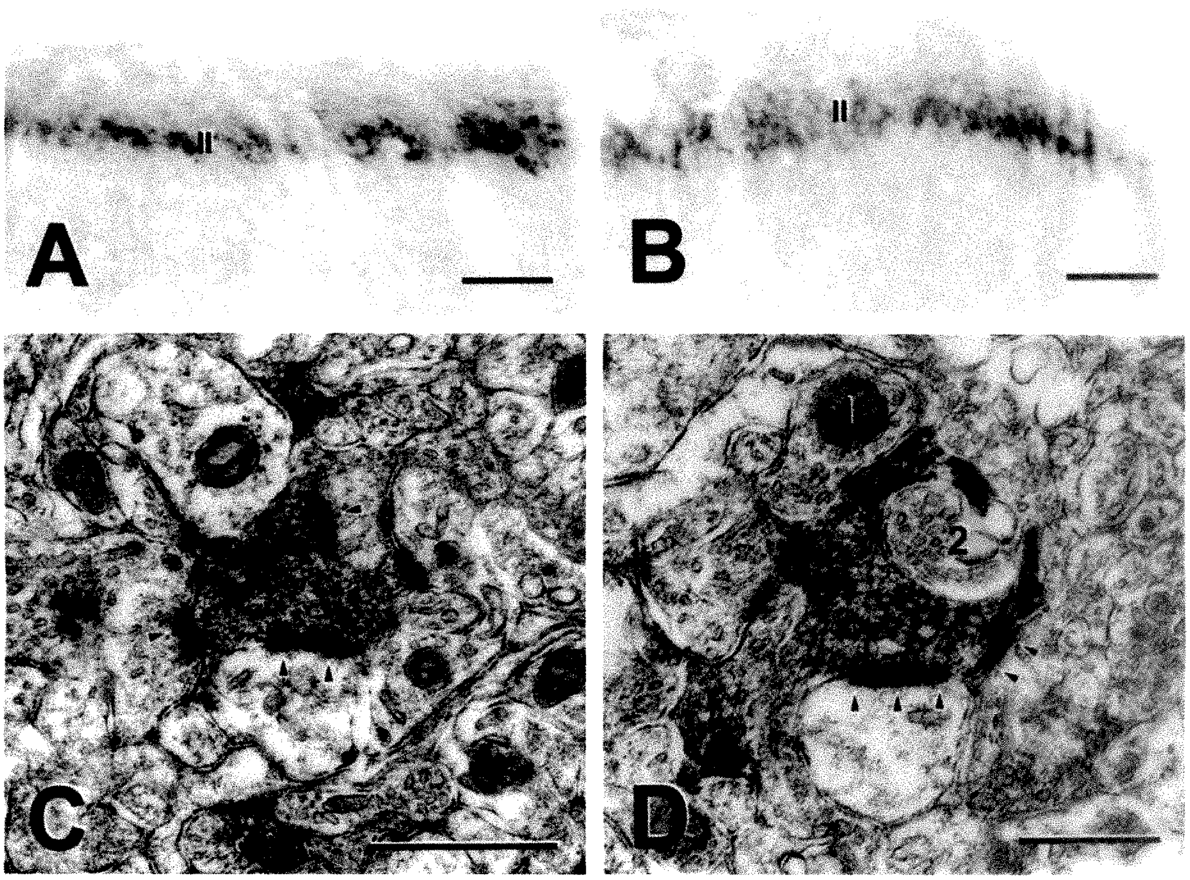


Fig 4 $P2X_3$ receptor immunoreactivity in the dorsal horn of the rat spinal cord (see also Fig. 5B). (A, B) A band of $P2X_3$ receptor immunoreactive terminals occurs in lamina II of the dorsal horn at the levels of both cervical (A) and lumbar (B) enlargements. Scale bars: 50 µm. (C) A $P2X_3$ receptor immunoreactive scalloped terminal in the cervical dorsal horn forms synapses (arrowheads) on three dendrites. Scale bar: 500 nm. (D) A $P2X_3$ receptor immunoreactive scalloped terminal in the cervical dorsal horn is presynaptic (arrowheads) to two dendrites and postsynaptic to two nerve processes (1, 2) that contain vesicles. Scale bar: 500 nm. (From Llewellyn-Smith and Burnstock, 1998.[94])

depressor reflex in anaesthetized rats.[100] Injection of α,β-methylene ATP evoked this reflex consisting of bradycardia, hypotension and apnoea, often preceded by hyperventilation. Suramin and PPADS antagonized the bradycardia and apnoeic components of the reflex, but not the vasopressor or hyperventilatory responses. P2 receptor agonism activated carotid chemoreceptor afferents (also described by Jarisch and colleagues[75] and McQueen and Ribeiro[101]), although this effect was unchanged by suramin and PPADS.

P2X receptors in CNS pain pathways

Spinal cord. The subcellular distribution of P2X purinoceptors is of particular interest with respect to a possible presynaptic role in the dorsal horn of the spinal cord. Evidence exists for purinergic transmission from nociceptors in the dorsal horn,[74] and it is possible that particular receptor subtypes play a specialized presynaptic role distinct from neuronal depolarization. There have been strong early indications that ATP acts as a neurotransmitter or neuromodulator in the spinal cord dorsal horn.[60 74 92 117 118] However, it is only recently that this has been clearly demonstrated.[2] Using transverse spinal cord slices from postnatal rats, excitatory postsynaptic currents have been shown to be mediated by P2X receptors, activated by synaptically released ATP, in a subpopulation of less than 5% of the neurones in lamina II, a region known to receive major input from nociceptive primary afferents. The P2X receptors on acutely dissociated dorsal horn neurones are non-desensitizing and are insensitive to α,β-methylene ATP and responses are antagonized by suramin and PPADS. This profile suggests they are of the $P2X_2$ receptor subtype or perhaps in heteromultimeric combination with $P2X_4$ or $P2X_6$. $P2X_3$ receptors appear to be largely located prejunctionally on sensory nerve terminals in lamina II (Fig. 4),[94] where there is evidence that they might modulate glutamate release.[65 66 70 93] Approximately half of the cultured spinal dorsal horn neurones were shown in a recent study[76] to use ATP as a fast excitatory neurotransmitter acting at ionotropic P2X postsynaptic receptors. ATP was not codetected with glutamate, but was coreleased with the

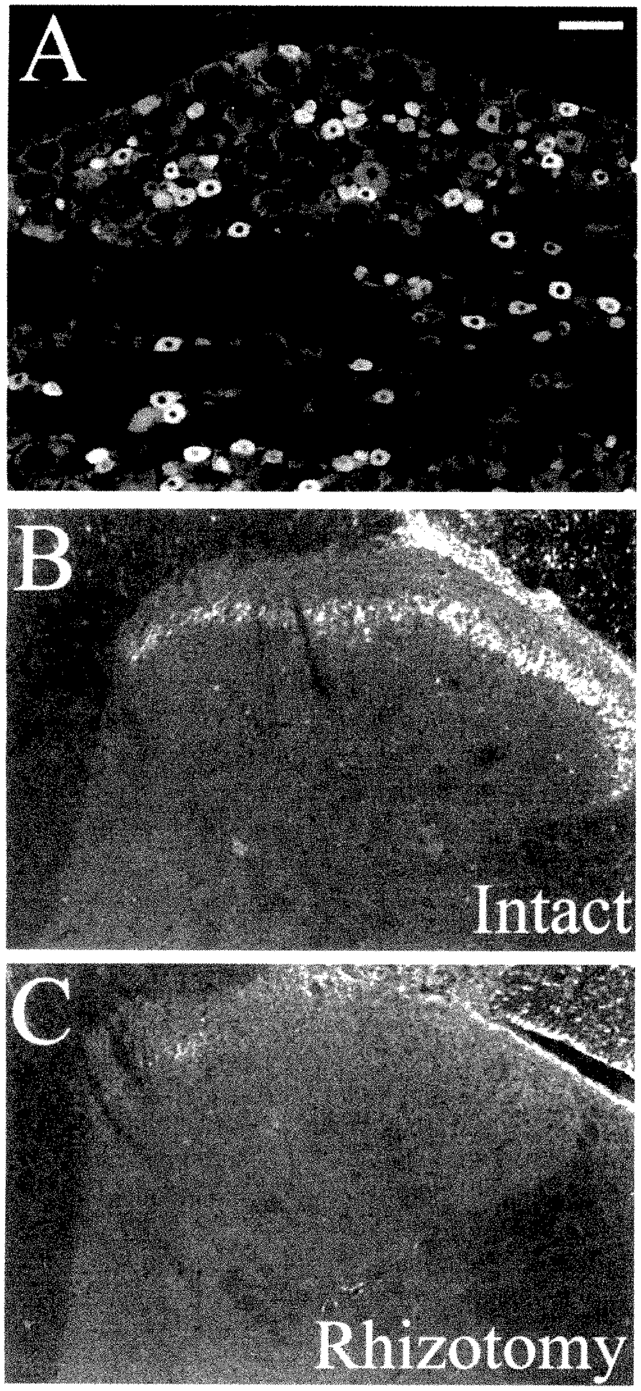


Fig 5 (A) P2X$_3$ receptor immunoreactivity in normal adult L5 DRG. Note that many small, but not large cells are immunopositive. (B) Immunoreactivity seen in the lumbar enlargement of the normal spinal cord. Specific P2X$_3$ receptor staining is present as a band across the entire width of lamina IIi of the dorsal horn and in fibres running in Lissauer's tract. (C) The loss of P2X$_3$ receptor immunoreactivity in the dorsal horn 2 weeks after rhizotomy of the L4 and L5 dorsal roots is shown. In B and C, the tyramide amplification technique has produced some nonspecific staining on the edges of the spinal cord and dorsal roots. Scale bar: 100 μm. (From Bradbury and colleagues, 1998.[16])

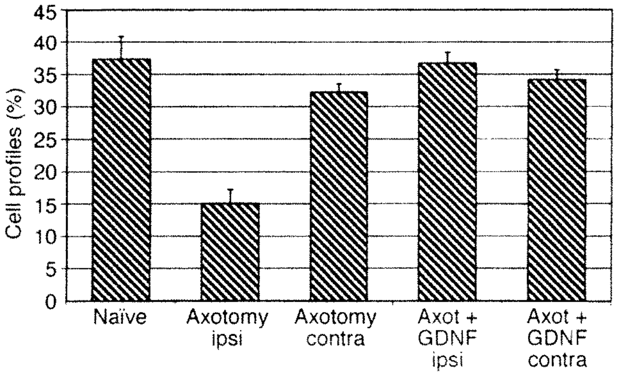


Fig 6 Histogram of the percentage of P2X$_3$ receptor-immunopositive cell profiles in the L4 and L5 of rat DRG under the following conditions: normal naive animals ($n = 4$), ipsilateral and contralateral to a sciatic nerve axotomy ($n = 7$), and ipsilateral and contralateral to a sciatic nerve axotomy but in rats treated with intrathecal glial-derived neurotrophic factor (GDNF, $n = 8$). The effects of axotomy are highly significant ($P<0.001$), while none of the other groups differ significantly from naive animals. (From Bradbury and colleagues, 1998.[16])

inhibitory neurotransmitter, GABA. It was speculated that differential modulation of the ATP and GABA components of cotransmission may help to explain changes in sensory message processing in the dorsal horn during mechanical hyperalgesia and neuropathic pain.

Brain. There is evidence from our laboratory of immunolocalization of P2X$_3$ receptors in the nucleus tractus solitarius.[94] P2X receptors have also been identified in rat trigeminal mesencephalic nucleus neurones, perhaps involved in processing proprioceptive information.[78]

Sources of ATP involved in pain transmission

It has been proposed that ATP released from different cell types is involved in the initiation of pain by acting on nociceptive purinoceptors on sensory nerve terminals (Fig. 9).[27 31]

In causalgia, reflex sympathetic dystrophy or 'sympathetically maintained pain' there appears to be sympathetic hyperinnervation (or hyperactivity), although the precise mechanisms involved are much debated.[99 122] It has been proposed that in these pathological conditions the ATP released from sympathetic nerves (as a cotransmitter with norepinephrine and neuropeptide Y)[24] acts on purinergic nociceptive sensory nerve endings, contributing to the initiation of pain.[27] The reports that surgical sympathectomy, sympathetic ganglion blockers and guanethidine (which prevents release of sympathetic cotransmitters) are more effective than adrenoceptor antagonists or reserpine (which depletes norepinephrine, but not ATP, from sympathetic nerve terminals) in preventing pain in these conditions are consistent with this hypothesis.[14 68 144]

Sympathetic nerve activity appears to be involved with other painful conditions, including the inflammation associated with arthritis.[87] As ATP induces prostaglandin synthesis (and prostaglandins are known to be mediators of inflammation), it has been suggested that ATP may play a further, indirect, role as a sympathetic cotransmitter in the generation of pain.[27] Merkel cells, which contain high

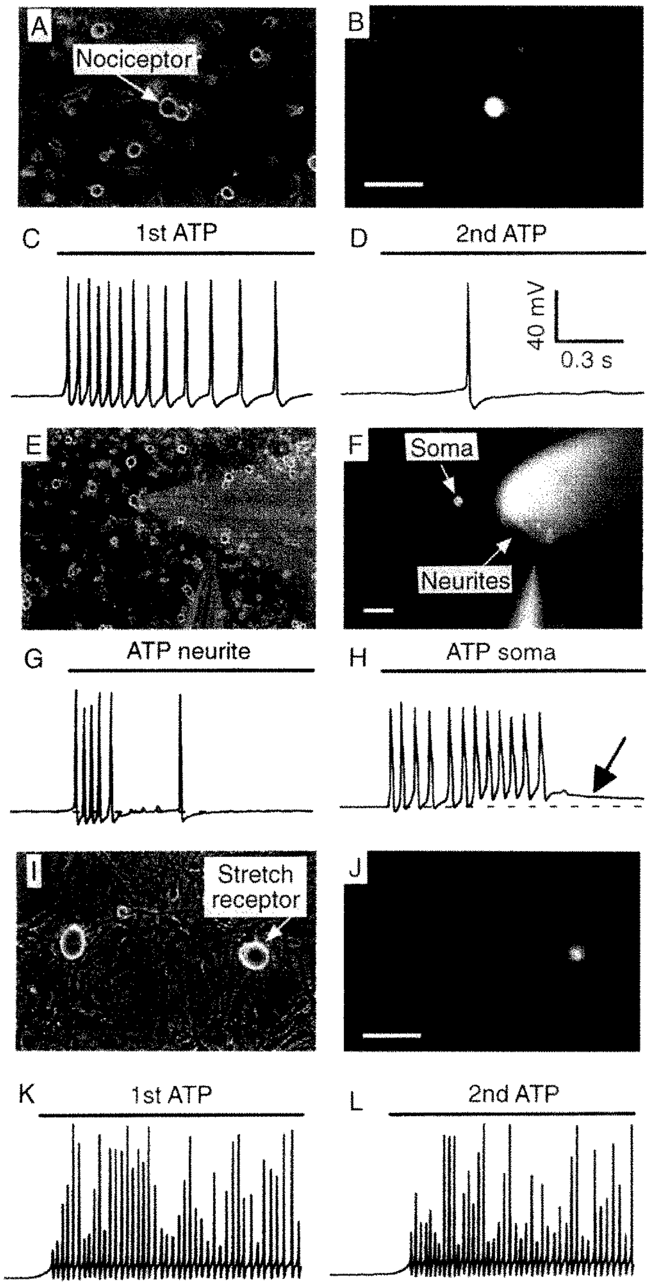


Fig 7 ATP (10 μM, 1 s) excited both nociceptive (tooth-pulp afferent) and non-nociceptive (muscle-stretch receptor) sensory neurones of the rat. (A) Corresponding phase micrograph, and (B) fluorescence micrograph (using fluorescent dye DiIC$_{18}$) of a nociceptor in primary culture. (C) ATP applied by puffer pipette to a labelled nociceptor triggered action potentials with diminishing frequency. (D) Response 1 min later; eight of twelve nociceptors had this adapting response; two others did not adapt and two responded to ATP with just a single action potential. (E) Phase micrograph and (F) fluorescence micrograph of a nociceptor, and recording and application pipettes. ATP application to neurites was visualized by the inclusion of fluorescent dye; bath solution flowed rightward. (G) Response to neuritic application. (H) Response to somal application included a sustained depolarization (arrow). (I) Phase and (J) fluorescence micrographs of a labelled muscle-stretch receptor. (K) Action potentials of stretch receptors did not adapt. (L) Response 1 min later; sampling rate (1 ms) was insufficient to capture all action potential peaks in K and L. In C and K ATP application was 5 min after ATP. Scale bars: 100 μm. (From Cook and colleagues, 1997.[43])

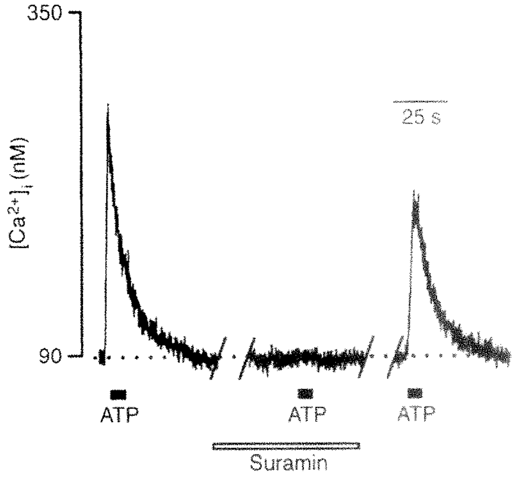


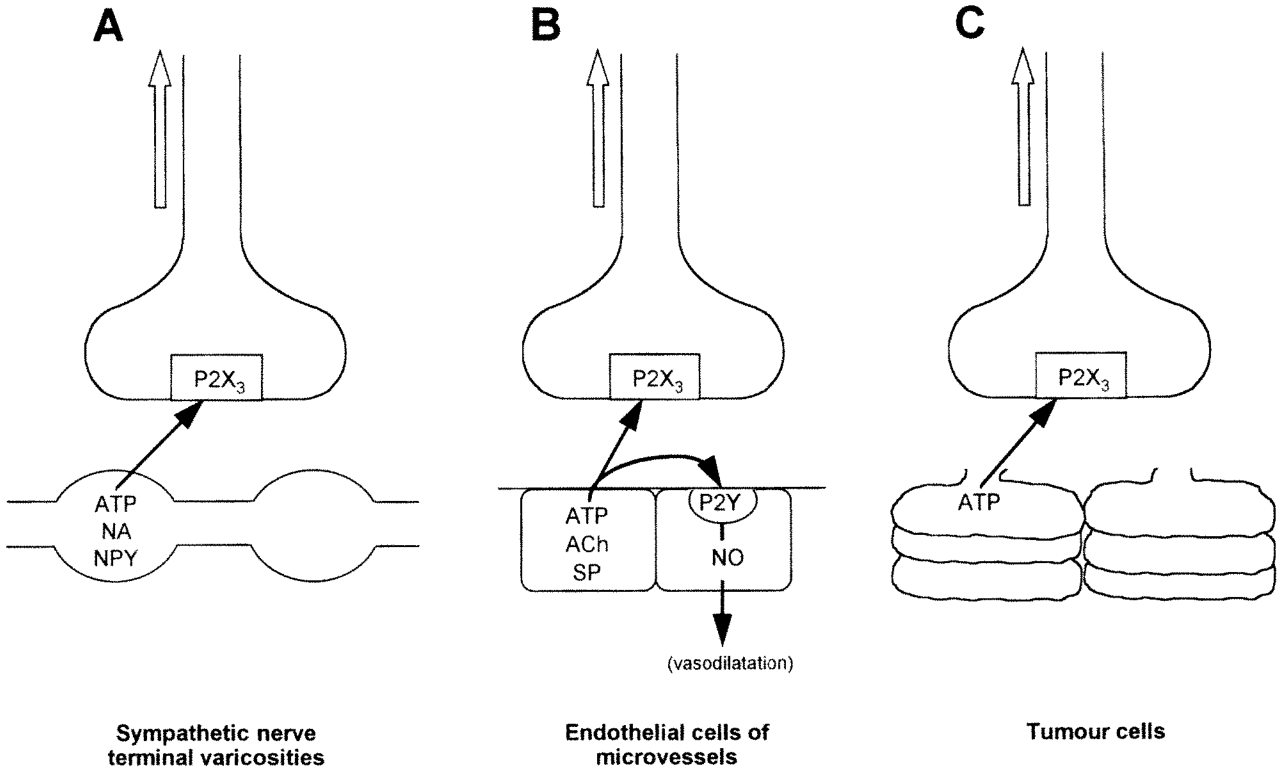
Fig 8 ATP-induced $[Ca^{2+}]_i$ transients in large dorsal root ganglion neurones from 2- to 3-month old mice are mediated through P2Y metabotropic receptors. The ATP-induced $[Ca^{2+}]_i$ transients (measured with the fluorescent dye Indo-1) are inhibited by suramin. ATP was applied in Ca^{2+}-free solution and the cell was incubated with 200 μM suramin for 5 min before administration of ATP. The response to ATP partially recovered after washout of suramin. (From Svichar and colleagues, 1997.[126])

concentrations of ATP, are closely associated with sensory nerve endings in the skin and may be another source of ATP involved in the maintenance of pain in reflex sympathetic dystrophy.[97]

Vascular pain—including angina, ischaemic muscle pain, migraine, lumbar pain and pelvic pain in women—appears to occur during the reactive hyperaemic phase that follows local vasospasm. In 1981, it was proposed that ATP may play a role in mediating these effects in migraine.[22] During reactive hyperaemia, large amounts of ATP are released from vascular endothelial cells that act on endothelial P2Y receptors, resulting in the release of nitric oxide and vasodilatation.[23] Burnstock[27] has proposed that in the microcirculation, ATP diffuses from the endothelial cells to activate nociceptive endings of sensory nerve fibres in the adventitia. A central role for adenosine has also been considered in relation to anginal pain.[46,128] ATP released from platelets during aggregation, which has been reported to increase in migraine, may also contribute to the initiation of pain via nociceptive purinoceptors. Consistent with this hypothesis is the recent report that nociception from blood vessels is independent of the sympathetic nervous system under physiological conditions in humans.[79]

Tumour cells are known to contain exceptionally high concentrations of ATP.[96,124] It has been suggested that when a tumour reaches a size that leads to breakage of cells during abrasive movements, the ATP released acts on nociceptive endings of sensory nerves in the vicinity, resulting in the sensation of pain.[27] ATP released from damaged muscle after major accidents or surgery could also be involved in local pain and in pain associated with traumatic shock.[131]

It has recently been proposed[31] that in tubes (including



Sympathetic nerve terminal varicosities

Endothelial cells of microvessels

Tumour cells

Fig 9 Schematic drawing of the sources of ATP acting on P2X$_3$ nociceptive receptors on sensory nerve terminals. (A) ATP released as a cotransmitter with norepinephrine (NA) and neuropeptide Y (NPY) from sympathetic nerve terminal varicosities. (B) ATP released from vascular endothelial cells of microvessels during reactive hyperaemia after local vasospasm to act both on P2X$_3$ receptors on sensory nerve terminals and P2Y receptors on endothelial cells leading to release of nitric oxide (NO) and subsequent vasodilatation. Note that acetylcholine (ACh) and substance P (SP) are also stored and released from endothelial cells during reactive hyperaemia. (C) ATP released from tumour cells damage during abrasive activity. (From Burnstock, 1996.[27])

ureter, salivary duct, bile duct, vagina and intestine) and sacs (including urinary bladder, gall bladder and lung) nociceptive mechanosensory transduction occurs where distension releases ATP from the epithelial cells lining these organs, which then activates P2X$_{2/3}$ receptors on subepithelial sensory nerve plexuses to relay messages to the CNS pain centres. Supporting evidence for this concept comes from studies of the rat bladder where ATP has been shown to be released from the urothelial cells by hydrostatic pressure changes,[57] and where nerve discharges were produced in pelvic nerve afferent from the bladder during slow distension and infusion of α,β-methylene ATP, which were antagonized by suramin.[104] There is also a report presenting evidence for the presence of P2X receptors on intestinal afferent nerve endings.[83]

Future directions

The search for selective antagonists at the P2X$_3$ receptor can be pursued now that the molecular structure of the nociceptor- associated P2X$_3$ receptor has been identified. Such antagonists could then be tested both on both recombinant receptors expressed in oocytes or transfected cells and *in vivo* models of different types of pain. Since P2X$_3$ receptors are clearly not the only receptors involved in pain, the possibility of synergy with receptors for other agents that modulate pain (such as bradykinin, histamine and 5-hydroxytryptamine) should be explored. In addition to the description in this review of ATP acting on receptors on sensory nerve terminals, there are reports that ATP acts on dorsal horn neurones in the spinal cord after being released from a subpopulation of small primary afferent nerves involved in pain pathways.[119] The future identification of a selective A$_1$ agonist to attenuate pain at the spinal cord level and of an A$_2$ antagonist at the sensory terminal level are also of obvious clinical interest.[121,123] Interactions with the recently identified acid sensory ion channel localized on small primary afferent neurones[111] will be of much interest. Further intriguing parallels that need to be explored concern capsaicin-gated channels and P2X nociceptive receptors, including the mechanism of desensitization through calcineuron action,[49,80] the pronounced pH-dependence of channel gating as well as the distribution and expression of capsaicin sensitivity at the P2X$_3$ receptor, and the ion selectivity of the channel.[85]

References

1 Abbracchio M, Burnstock G. Purinoceptors: are there families of P$_{2X}$ and P$_{2Y}$ purinoceptors? *Pharmacol Ther* 1994; **64**: 445–75

2 Bardoni R, Goldstein PA, Lee CJ, Gu JG, MacDermott AB. ATP P$_{2X}$ receptors mediate fast synaptic transmission in the dorsal horn of the rat spinal cord. *J Neurosci* 1997; **17**: 5297–304

3 Barnard EA, Burnstock G, Webb TE. G protein-coupled receptors for ATP and other nucleotides: a new receptor family. *Trends Pharmacol Sci* 1994; **15**: 67–70

4 Barnard EA, Webb TE, Simon J, Kunapuli SP. The diverse series of recombinant P2Y purinoceptors. *Ciba Found Symp* 1996; **198**: 166–80

5 Bean BP, Friel DD. ATP-activated channels in excitable cells. *Ion Channels* 1990; **2**: 169–203

6 Benham CD, Tsien RW. A novel receptor-operated Ca^{2+}-permeable channel activated by ATP in smooth muscle. *Nature* 1987; **328**: 275–8

7 Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow *Am J Physiol* 1963; **204**: 317–22

8 Bland-Ward PA, Humphrey PPA. Acute nociception mediate by hindpaw P2X receptor activation in the rat. *Br J Pharmacol* 1997; **122**: 365–71

9 Bleehen T. The effects of adenine nucleotides on cutaneous afferent nerve activity. *Br J Pharmacol* 1978; **62**· 573–7

10 Bleehen T, Keele CA Observations on the algogenic actions of adenosine compounds on human blister base preparation *Pain* 1977; **3**. 367–77

11 Bo X, Alavi A, Xiang Z, Oglesby IB, Ford APDW, Burnstock G. Localization of $P2X_2$ and $P2X_3$ receptor immunoreactive nerves in rat taste buds. *Neuroreport* 1999; **10**: 1107–11

12 Bo X, Burnstock G Distribution of $[^3H]\alpha,\beta$-methylene ATP binding sites in rat brain and spinal cord. *Neuroreport* 1994; **5**: 1601–4

13 Boarder MR, Weisman GA, Turner JT, Wilkinson GF. G protein-coupled P2 purinoceptors· from molecular biology to functional responses. *Trends Pharmacol Sci* 1995; **16**: 133–9

14 Bonezzi C, Miotti D, Bettaglio R, Stephen R Electromotive administration of guanethidine for treatment of reflex sympathetic dystrophy. a pilot study in eight patients. *J Pain Symptom Manage* 1994; **9**: 39–43

15 Bouvier MM, Evans ML, Benham CD. Calcium influx induced by stimulation of ATP receptors on neurons cultured from rat dorsal root ganglia. *Eur J Neurosci* 1991, **3**: 285–91

16 Bradbury EJ, Burnstock G, McMahon SB. The expression of $P2X_3$ purinoceptors in sensory neurons. effects of axotomy and glial-derived neurotrophic factor. *Mol Cell Neurosci* 1998; **12**: 256–68

17 Brake AJ, Wagenbach MJ, Julius D. New structural motif for ligand-gated ion channels defined by an inotropic ATP receptor. *Nature* 1994; **371**. 519–23

18 Burnstock G. Evolution of the autonomic innervation of visceral and cardiovascular systems in vertebrates. *Pharmacol Rev* 1969; **21**: 247–324

19 Burnstock G Purinergic nerves. *Pharmacol Rev* 1972; **24**: 509–81

20 Burnstock G. Do some nerve cells release more than one transmitter? *Neuroscience* 1976; **1**: 239–48

21 Burnstock G. A basis for distinguishing two types of purinergic receptor In: Straub RW, Bolis L, eds. *Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach*. New York: Raven Press, 1978, 107–18

22 Burnstock G. Pathophysiology of migraine: a new hypothesis. *Lancet* 1981; **i**. 1397–9

23 Burnstock G. Local mechanisms of blood flow control by perivascular nerves and endothelium *J Hypertens* 1990; **8** (Suppl. 7): S95–6

24 Burnstock G. Co-transmission The Fifth Heymans Lecture—Ghent, February 17, 1990. *Arch Int Pharmacodyn Ther* 1990; **304**: 7–33

25 Burnstock G. Hypoxia, endothelium and purines *Drug Dev Res* 1993; **28**: 301–5

26 Burnstock G. Noradrenaline and ATP. cotransmitters and neuromodulators. *J Physiol Pharmacol* 1995; **46**: 365–84

27 Burnstock G. A unifying purinergic hypothesis for the initiation of pain. *Lancet* 1996; **347**: 1604–5

28 Burnstock G. P2 Purinoceptors: historical perspective and classification. In. Chadwick DJ, Goode JA, eds. *P2 Purinoceptors· Localization, Function and Transduction Mechanisms*. Chichester. John Wiley and Sons, 1996; 1–29

29 Burnstock G. (Guest Editor). Purinergic neurotransmission. *Semin Neurosci* 1996; **8**: 171–257

30 Burnstock G. The past, present and future of purine nucleotides as signalling molecules. *Neuropharmacology* 1997, **36**: 1127–39

31 Burnstock G. Release of vasoactive substances from endothelial cells by shear stress and purinergic mechano-sensory transduction. *J Anat* 1999; **194**: 335–42

32 Burnstock G, Campbell G, Bennett M, Holman ME. The effects of drugs on the transmission of inhibition from autonomic nerves to the smooth muscle of the guinea pig taenia coli *Biochem Pharmacol* 1963; **12** (Suppl.): 134–5

33 Burnstock G, Campbell G, Bennett M, Holman ME Innervation of the guinea-pig taenia coli: are there intrinsic inhibitory nerves which are distinct from sympathetic nerves? *Int J Neuropharmacol* 1964; **3**: 163–6

34 Burnstock G, Campbell G, Satchell D, Smythe A. Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br J Pharmacol* 1970, **40**: 668–88

35 Burnstock G, Fischer B, Hoyle CHV *et al.* Structure–activity relationships for derivatives of adenosine 5′-triphosphate as agonists at P_2 purinoceptors: heterogeneity within P_{2X} and P_{2Y} subtypes. *Drug Dev Res* 1994; **31**: 206–19

36 Burnstock G, Kennedy C. Is there a basis for distinguishing two types of P_2-purinoceptor? *Gen Pharmacol* 1985; **16**: 433–40

37 Burnstock G, King BF. Numbering of cloned P2 purinoceptors. *Drug Dev Res* 1996; **38**: 67–71

38 Burnstock G, Wood JN. Purinergic receptors: their role in nociception and primary afferent neurotransmission. *Curr Opin Neurobiol* 1996, **6**: 526–32

39 Chen C-C, Akopian AN, Sivilotti L, Colquhoun D, Burnstock G, Wood JN. A P2X purinoceptor expressed by a subset of sensory neurons. *Nature* 1995; **377**: 428–31

40 Collo G, North RA, Kawashima E *et al.* Cloning of $P2X_5$ and $P2X_6$ receptors and the distribution and properties of an extended family of ATP-gated ion channels. *J Neurosci* 1996; **16**· 2495–507

41 Communi D, Parmentier M, Boeynaems J-M Cloning, functional expression and tissue distribution of the human $P2Y_6$ receptor *Biochem Biophys Res Commun* 1996; **222**· 303–8

42 Cook SP, McCleskey EW. Desensitization, recovery and Ca^{2+}-dependent modulation of ATP-gated P2X receptors in nociceptors. *Neuropharmacology* 1997; **36**. 1303–8

43 Cook SP, Vulchanova L, Hargreaves KM, Elde R, McCleskey EW Distinct ATP receptors on pain-sensing and stretch-sensing neurons. *Nature* 1997; **387**: 505–8

44 Cook SP, Rodland KD, McCleskey EW. A memory for extracellular Ca^{2+} by speeding recovery of P2X receptors from desensitization *J Neurosci* 1998; **18**. 9238–44

45 Coutts AA, Jorizzo JL, Eady RAJ, Greaves MW, Burnstock G. Adenosine triphosphate-evoked vascular changes in human skin. mechanism of action. *Eur J Pharmacol* 1981; **76**· 391–401

46 Crea F, Gaspardone A. New look to an old symptom angina pectoris. *Circulation* 1997; **96**: 3766–73

47 De Mey J, Burnstock G, Vanhoutte PM Modulation of the evoked release of noradrenaline in canine saphenous vein via presynaptic receptors for adenosine but not ATP. *Eur J Pharmacol* 1979; **55**: 401–5

48 De Mey JG, Vanhoutte PM. Role of the intima in cholinergic and purinergic relaxation of isolated canine femoral arteries. *J Physiol* 1981; **316**: 347–55

49 Docherty RJ, Yeas JC, Bevan S, Boddeke HWGM. Inhibition of calcineurin inhibits the desensitization of capsaicin-evoked currents in cultured dorsal root ganglion neurons from adult rats. *Pflugers Arch* 1996; **431**: 828–37

50 Dowd E, McQueen DS, Chessell IP, Humphrey PPA. P2X receptor-mediated excitation of nociceptive afferents in the normal and arthritic rat knee joint. *Br J Pharmacol* 1998; **125**: 341–6

51 Driessen B, Reimann W, Selve N, Friderichs E, Bültmann R. Antinociceptive effect of intrathecally administered P2-purinoceptor antagonists in rats. *Brain Res* 1994; **666**: 182–8

52 Drury AN, Szent-Gyorgyi A. The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. *J Physiol* 1929; **68**: 213–37

53 Dubyak GR. Signal transduction by P_2-purinergic receptors for extracellular ATP. *Am J Resp Cell Mol Biol* 1991; **4**: 295–300

54 Eccles JC. *The Physiology of Synapses*. Berlin: Springer Verlag, 1964; 1–316

55 Emmelin N, Feldberg W. Systemic effects of adenosine triphosphate. *Br J Pharmacol* 1948; **3**: 213–23

56 Eriksson J, Bongenhielm U, Kidd E, Matthews B, Fried K. Distribution of $P2X_3$ receptors in the rat trigeminal ganglion after inferior alveolar nerve injury. *Neurosci Lett* 1998; **254**: 37–40

57 Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes—a possible sensory mechanism? *J Physiol* 1997; **505**: 503–11

58 Fredholm BB, Abbracchio MP, Burnstock G *et al.* VI. Nomenclature and classification of purinoceptors. *Pharmacol Rev* 1994; **46**: 143–56

59 Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373–6

60 Fyffe REW, Perl ER. Is ATP a central synaptic mediator for certain primary afferent fibres from mammalian skin? *Proc Natl Acad Sci USA* 1984; **81**: 6890–3

61 Garcia-Guzman M, Stuhmer W, Soto F. Molecular characterization and pharmacological properties of the human $P2X_3$ purinoceptor. *Brain Res Mol Brain Res* 1997; **47**: 59–66

62 Gomaa AA. Characteristics of analgesia induced by adenosine triphosphate. *Pharmacol Toxicol* 1987; **61**: 199–202

63 Gordon JL. Extracellular ATP: effects, sources and fate. *Biochem J* 1986; **233**: 309–19

64 Green PG, Basbaum AI, Helms C, Levine JD. Purinergic regulation of bradykinin-induced plasma extravasation and adjuvant-induced arthritis in the rat. *Proc Natl Acad Sci USA* 1991; **88**: 4162–5

65 Gu JG, Bardoni R, Magherini PC, MacDermott AB. Effects of the P_2-purinoceptor antagonists suramin and pyridoxal-phosphate-6-azophenyl-2′,4′-disulfonic acid on glutamatergic synaptic transmission in rat dorsal horn neurons of the spinal cord. *Neurosci Lett* 1998; **253**: 167–70

66 Gu JG, MacDermott AB. Activation of ATP P2X receptors elicits glutamate release from sensory neuron synapses. *Nature* 1997; **389**: 749–53

67 Hamilton SG, Wade A, McMahon SB. The effects of inflammatory mediators on nociceptive behaviour induced by ATP analogues in the rat. *Br J Pharmacol* 1999; **126**: 326–32

68 Hannington Kiff JG. Intravenous regional sympathetic block with guanethidine. *Lancet* 1974; **I**: 1019–20

69 Harden TK, Boyer JL, Nicholas RA. P2-purinergic receptors: subtype-associated signaling responses and structure. *Annu Rev Pharmacol Toxicol* 1995; **35**: 541–79

70 Ho BT, Huo YY, Lu JG, Newman RA, Levin VA. Analgesic activity of anti-cancer agent suramin. *Anticancer Drugs* 1992; **3**: 91–4

71 Holton P. The liberation of adenosine triphosphate on antidromic stimulation of sensory nerves. *J Physiol* 1959; **145**: 494–504

72 Hu HZ, Li ZW. Substance P potentiates ATP-activated currents in rat primary sensory neurons. *Brain Res* 1996; **739**: 163–8

73 Hu H-Z, Li Z-W. Modulation by adenosine of GABA-activated current in rat dorsal root ganglion neurons. *J Physiol* 1997; **501**: 67–75

74 Jahr CE, Jessell TM. ATP excites a subpopulation of rat dorsal horn neurones. *Nature* 1983; **304**: 730–3

75 Jarisch A, Landgren S, Neil E, Zotterman G. Impulse activity in the carotid sinus nerve following intracarotid injection of potassium chloride, veratrine sodium citrate, adenosine triphosphate and α-dinitrophenol. *Acta Physiol Scand* 1952; **25**: 195–211

76 Jo Y-H, Schlichter R. Synaptic corelease of ATP and GABA in cultured spinal neurons. *Nature Neurosci* 1998; **2**: 241–5

77 Kennedy C, Leff P. How should P2X purinoceptors be classified pharmacologically? *Trends Pharmacol Sci* 1995; **16**: 168–74

78 Khakh BS, Humphrey PP, Henderson G. ATP-gated cation channels (P2X purinoceptors) in trigeminal mesencephalic nucleus neurons of the rat. *J Physiol* 1997; **498**: 709–15

79 Kindgen-Milles D, Holthusen H. Nociception from blood vessels is independent of the sympathetic nervous system under physiological conditions in humans. *Eur J Pharmacol* 1997; **328**: 41–4

80 King B, Chen C, Akopian AN, Burnstock G, Wood JN. A role for calcineurin in the desensitization of the $P2X_3$ receptor. *Neuroreport* 1997; **8**: 1099–102

81 King BF, Townsend-Nicholson A, Burnstock G. Metabotropic receptors for ATP and UTP: exploring the correspondence between native and recombinant nucleotide receptors. *Trends Pharmacol Sci* 1998; **19**: 506–14

82 King BF, Ziganshina LE, Pintor J, Burnstock G. Full sensitivity of $P2X_2$ purinoceptor to ATP revealed by changing extracellular pH. *Br J Pharmacol* 1996; **117**: 1371–3

83 Kirkup AJ, Booth CE, Chessell IP, Humphrey PPA, Grundy D. Excitatory effect of P2X receptor activation on mesenteric afferent nerves in the anaesthetised rat. *J Physiol* 1999; **520**: 551–63

84 Krishtal OA, Marchenko SM, Obukhov AG, Volkova TM. Receptors for ATP in rat sensory neurones: the structure–function relationship for ligands. *Br J Pharmacol* 1988; **95**: 1057–62

85 Krylova O, Chen CC, Akopian A, Souslova V, Okuse K, Abson N, Ravenall S, Wood JN. Ligand-gated ion channels of sensory neurons: from purines to peppers. *Biochem Soc Trans* 1997; **25**: 842–4

86 Lê K-T, Villeneuve P, Ramjaun AR, McPherson PS, Beaudet A, Seguela P. Sensory presynaptic and widespread somatodendritic immunolocalization of central ionotropic P2X ATP receptors. *Neuroscience* 1998; **83**: 177–90

87 Levine JD, Goetzl EJ, Basbaum AI. Contribution of the nervous system to the pathophysiology of rheumatoid arthritis and other polyarthrites. *Rheum Dis Clin North Am* 1987; **13**: 369–83

88 Lewis C, Neidhart S, Holy C, North RA, Surprenant A. Coexpression of $P2X_2$ and $P2X_3$ receptor subunits can account for ATP-gated currents in sensory neurons. *Nature* 1995; **377**: 432–5

89 Li C, Peoples RW, Weight FF. Acid pH augments excitatory action of ATP on a dissociated mammalian sensory neuron. *Neuroreport* 1996; **7**: 2151–4

90 Li C, Peoples RW, Weight FF. Enhancement of ATP-activated current by protons in dorsal root ganglion neurons *Pflugers Arch* 1997, **433**: 446–54

91 Li C, Peoples RW, Weight FF. Mg^{2+} inhibition of ATP-activated current in rat nodose ganglion neurons: evidence that Mg^{2+} decreases the agonist affinity of the receptor. *J Neurophysiol* 1997; **77**: 3391–5

92 Li J, Perl ER. ATP modulation of synaptic transmission in the spinal substantia gelatinosa *J Neurosci* 1995; **15**: 3357–65

93 Li P, Calejesan AA, Zhou M. ATP P2X receptors and sensory synaptic transmission between afferent fibers and spinal dorsal horn neurons in rats. *J Neurophysiol* 1998; **80**. 3356–60

94 Llewellyn-Smith IJ, Burnstock G Ultrastructural localization of P2X$_3$ receptors in rat sensory neurons. *Neuroreport* 1998; **9**: 2245–50

95 Lustig KD, Shiau AK, Brake AJ, Julius D. Expression cloning of an ATP receptor from mouse neuroblastoma cells. *Proc Natl Acad Sci USA* 1993; **90**: 5113–7

96 Maehara Y, Kusumoto H, Anai H, Kusumoto T, Sugimachi K. Human tumor tissues have higher ATP contents than normal tissues. *Clin Chim Acta* 1987; **169**: 341–3

97 Malinovsky L, Pac L. Is the Merkel cell a secondary sensory cell? (A contribution to the classification of Merkel cell neurite complexes.) *Z Mikrosk Anat Forsch* 1985; **99**: 119–28

98 Martinson J, Muren A Excitatory and inhibitory effects of vagus stimulation on gastric motility in the cat. *Acta Physiol Scand* 1963; **57**: 309–16

99 McMahon SB. Mechanisms of cutaneous, deep and visceral pain. In. Wall PD, Melzack R, eds. *Textbook of Pain*. London: Churchill Livingstone, 1994; 129–51

100 McQueen DS, Bond SM, Moores C, Chessell I, Humphrey PPA, Dowd E. Activation of P2X receptors for adenosine triphosphate evokes cardiorespiratory reflexes in anaesthetized cats. *J Physiol* 1998; **507**: 843–55

101 McQueen DS, Ribeiro JA. On the specificity and type of receptor involved in carotid body chemoreceptor activation by adenosine in the cat. *Br J Pharmacol* 1983; **80**. 347–54

102 Mello CF, Begnini J, De La Vega DD *et al.* Antinociceptive effect of purine nucleotides. *Braz J Med Biol Res* 1996; **29**: 1379–87

103 Moody CJ, Meghji P, Burnstock G. Stimulation of P$_1$-purinoceptors by ATP depends partly on its conversion to AMP and adenosine and partly on direct action. *Eur J Pharmacol* 1984; **97**: 47–54

104 Morrison JFB, Namasivayam S, Eardley I. ATP may be a natural modulator of the sensitivity of bladder mechanoreceptors during slow distention. *Proceedings of the 1st International Consultation on Incontinence* 1998; 84 (Abstract)

105 Nakamura F, Strittmatter SM P2Y$_1$ purinergic receptors in sensory neurons: Contribution to touch-induced impulse generation. *Proc Natl Acad Sci USA* 1996, **93**. 10465–70

106 Nguyen T, Erb L, Weisman GA *et al.* Cloning, expression, and chromosomal localization of the human uridine nucleotide receptor gene. *J Biol Chem* 1995; **270**: 30845–8

107 Nicke A, Baumert HG, Rettinger J *et al.* P2X$_1$ and P2X$_3$ receptors form stable trimers: a novel structural motif of ligand-gated ion channels. *EMBO J* 1998; **17**. 3016–28

108 North RA. P2X purinoceptor plethora. *Semin Neurosci* 1996; **8** 187–95

109 North RA, Barnard EA. Nucleotide receptors. *Curr Opin Neurobiol* 1997; **7**: 346–57

110 O'Connor SE, Dainty IA, Leff P. Further subclassification of ATP receptors based on agonist studies. *Trends Pharmacol Sci* 1991; **12**: 137–41

111 Olson TH, Riedl MS, Vulchanova L, Ortiz-Gonzalez XR, Elde R. An acid sensing ion channel (ASIC) localizes to small primary afferent neurons in rats. *Neuroreport* 1998; **9**: 1109–13

112 Pelleg A, Hurt CM. Mechanism of action of ATP on canine pulmonary vagal C-fiber nerve terminals. *J Physiol* 1996; **490**: 265–75

113 Pelleg A, Hurt CM, Michelson EL. Cardiac effects of adenosine and ATP. *Ann NY Acad Sci* 1990; **603**: 19–30

114 Pintor J, Miras-Portugal MT. Diadenosine polyphosphates (ApxA) as new neurotransmitters. *Drug Dev Res* 1993; **28** 259–62

115 Rae MG, Rowan EG, Kennedy C Pharmacological properties of P2X$_3$-receptors present in neurones of the rat dorsal root ganglia. *Br J Pharmacol* 1998; **124**. 176–80

116 Robertson SJ, Rae MG, Rowan EG, Kennedy C Characterization of a P2X-purinoceptor in cultured neurones of the rat dorsal root ganglia. *Br J Pharmacol* 1996, **118**. 951–6

117 Salter MW, Henry JL Effects of adenosine 5′-monophosphate and adenosine 5′-triphosphate on functionally identified units in the cat spinal dorsal horn. Evidence for a differential effect of adenosine 5′-triphosphate on nociceptive vs non-nociceptive units. *Neuroscience* 1985; **15**: 815–25

118 Salter MW, Hicks JL. ATP-evoked increases in intracellular calcium in neurons and glia from the dorsal spinal cord *J Neurosci* 1994; **14**. 1563–75

119 Sawynok J. Purines and nociception. In Jacobson KA, Jarvis MF, eds. *Purinergic Approaches in Experimental Therapeutics* New York: Wiley–Liss Inc., 1997; 495–513

120 Sawynok J, Reid A Peripheral adenosine 5′-triphosphate enhances nociception in the formalin test via activation of a purinergic P$_{2X}$ receptor *Eur J Pharmacol* 1997; **330**: 115–21

121 Sawynok J, Doak G, Poon A. Adenosine and pain. recent findings with directly and indirectly acting agents. *Drug Dev Res* 1998; **45**: 304–11

122 Schott GD. Pain and the sympathetic nervous system In: Bannister R, Mathias CJ, eds. *Autonomic Failure*. Oxford. Oxford University Press, 1992; 904–17

123 Segerdahl M, Sollevi, A. Adenosine and pain relief a clinical overview. *Drug Dev Res* 1998; **45**: 151–8

124 Siems WG, Grune T, Schmidt H, Tikhonov YV, Pimenov AM. Purine nucleotide levels in host tissues of Ehrlich ascites tumor-bearing mice in different growth phases of the tumor. *Cancer Res* 1993; **53**: 5143–7

125 Surprenant A, Rassendren F, Kawashima E, North RA, Buell G. The cytolytic P$_{2Z}$ receptor for extracellular ATP identified as a P$_{2X}$ receptor (P2X$_7$). *Science* 1996; **272**. 735–8

126 Svichar N, Shmigol A, Verkhratsky A, Kostyuk P. ATP induces Ca^{2+} release from IP$_3$-sensitive Ca^{2+} stores exclusively in DRG neurones. *Neuroreport* 1997; **8**. 1555–9

127 Svichar N, Shmigol A, Verkhratsky A, Kostyuk P. InsP$_3$-induced Ca^{2+} release in dorsal root ganglion neurones *Neurosci Lett* 1997; **227**: 107–10

128 Sylvén C. Mechanisms of pain in angina pectoris—a critical review of the adenosine hypothesis. *Cardiovasc Drugs Ther* 1993; **7**: 745–59

129 Thomas S, Virginio C, North RA, Surprenant A. The antagonist trinitrophenyl-ATP reveals co-existence of distinct P2X receptor channels in rat nodose neurones *J Physiol* 1998; **509**: 411–7

130 Tjølsen A, Berge O-G, Hunskaar S, Rosland JH, Hole K The formalin test: an evaluation of the method. *Pain* 1992; **51**: 5–17

131 Trams EJ, Kauffman H, Burnstock G. A proposal for the role of ecto-enzymes and adenylates in traumatic shock. *J Theor Biol* 1980; **87** 609–21

132 Trezise DJ, Humphrey PPA Activation of cutaneous afferent neurones by ATP. In: Olesen J, Moscowitz MA, eds *Experimental*

Headache Models. Frontiers in Headache Research, Vol 6 New York: Raven Press, 1997, 111–6

133 Ueno S, Tsuda M, Iwanaga T, Inoue K. Cell type-specific ATP-activated responses in rat dorsal root ganglion neurons. *Br J Pharmacol* 1999; **126**: 429–36

134 Valera S, Hussy N, Evans RJ *et al.* A new class of ligand-gated ion channel defined by P_{2X} receptor for extra-cellular ATP. *Nature* 1994; **371**: 516–9

135 van Rhee AM, Fischer B, Van Galen PJ, Jacobson KA. Modelling the P2Y purinoceptor using rhodopsin as template. *Drug Design Disc* 1995; **13**: 133–54

136 Virginio C, North RA, Surprenant A. Calcium permeability and block at homomeric and heteromeric P2X$_2$ and P2X$_3$ receptors, and P2X receptors in rat nodose neurones. *J Physiol* 1998; **510**: 27–35

137 Virginio C, Robertson G, Surprenant A, North RA. Trinitrophenyl-substituted nucleotides are potent antagonists selective for P2X$_1$, P2X$_3$ and heteromeric P2X$_{2/3}$ receptors. *Mol Pharmacol* 1998; **53**: 969–73

138 Vulchanova L, Arvidsson U, Riedl M *et al.* Differential distribution of two ATP-gated channels (P2X receptors) determined by imunocytochemistry. *Proc Natl Acad Sci USA* 1996; **93**: 8063–7

139 Vulchanova L, Arvidsson U, Riedl M *et al.* Imunocytochemical study of the P2X$_2$ and P2X$_3$ receptor subunits in rat and monkey sensory neurons and their central terminals. *Neuropharmacology* 1997; **36**: 1229–42

140 Vulchanova L, Riedl M, Shuster SJ *et al.* P2X$_3$ is expressed by DRG neurons that terminate in inner lamina II. *Eur J Neurosci* 1998; **10**: 3470–8

141 Webb TE, Simon J, Krishek BJ *et al.* Cloning and functional expression of a brain G-protein coupled ATP receptor. *FEBS Lett* 1993; **324**: 219–25

142 Wildman SS, King BF, Burnstock G. Zn^{2+} modulation of ATP-responses at recombinant P2X$_2$ receptors and its dependence on extracellular pH. *Br J Pharmacol* 1998; **123**: 1214–20

143 Xiang Z, Bo X, Burnstock G. Localization of ATP-gated P2X receptor immunoreactivity in rat sensory and sympathetic ganglia. *Neurosci Lett* 1998; **256**: 105–8

144 Yasuda JM. Guanethidine for reflex sympathetic dystrophy. *Ann Pharmacother* 1994; **28**: 338–41

British Journal of Anaesthesia 84 (4): 489–90 (2000)

BJA

SHORT COMMUNICATIONS

Randomized placebo-controlled trial to assess the effect of remifentanil and propofol on bispectral index and sedation

A. N. Strachan* and N. D. Edwards

University Department of Anaesthesia, Northern General Hospital, Herries Road, Sheffield S5 7AU, UK

**Corresponding author*

The effect of the combination of opiates and hypnotics on bispectral index (BIS) is unclear. This double-blind placebo-controlled trial investigated the effect on BIS and sedation of different infusion doses of remifentanil combined with a steady infusion of propofol. Forty patients initially received a target-controlled infusion of propofol 2 $\mu g\ ml^{-1}$ for 15 min. They were then randomized to receive either placebo, 0.01, 0.05 or 0.1 $\mu g\ kg^{-1}\ min^{-1}$ remifentanil for a further 15 min. We found a significant correlation between the dose of remifentanil and the change of BIS after 15 min of infusion. The correlation between all the sedation scores and their corresponding BIS was also significant. We concluded that remifentanil, in combination with propofol, reduces BIS when used for sedation.

Br J Anaesth 2000; **84**: 489–90

Keywords: measurement techniques, bispectral index; analgesics opioid, remifentanil; sedation

Accepted for publication: November 1, 1999

Bispectral index (BIS) is a processed EEG measurement which correlates with the sedation properties of single anaesthetic agents.[1–3] When more than one agent is used, such as a combination of an anaesthetic agent with an opiate, this simple relationship becomes less predictable.[4] Combinations of hypnotics and opiates have become a commonly used for sedation. We were interested in the effect upon BIS of such a combination of drugs. We investigated the effect on BIS and sedation of different infusion doses of remifentanil combined with a steady infusion of propofol.

Methods and results

After Local Ethical Committee approval and informed signed consent, we recruited 40 patients who were to undergo routine operations requiring general anaesthesia. Patients were aged between 16 and 80 yr and ASA I or II. Patients were excluded if they were epileptic, taking cerebrally active medications, required rapid sequence induction or were not within 20% of ideal body weight. No patients were premedicated.

The study took place in the anaesthetic room for 30 min before surgery. The first anaesthetist recorded the BIS data and sedation scores and took venous blood samples. A bifrontal montage was used (F7, F8, reference Fp2) for acquisition of BIS, using an Aspect-1000 monitor (software v.2.51; Aspect Medical Systems, Framingham, MA, USA). A baseline of 5 min of BIS was recorded before the start of the study period. The second anaesthetist recorded the arterial pressure, heart rate, arterial oxygen saturation and respiratory rate every 5 min during the study period, and applied airway maintenance manoeuvres if appropriate. Oxygen was given via a facemask.

At the start of the study all patients received a target controlled infusion of propofol 2 $\mu g\ ml^{-1}$ from a Graseby 'Diprifuser' pump for 15 min. By means of blocked randomization of sealed envelopes, patients were allocated, in a double-blind fashion, to receive placebo, 0.01, 0.05 or 0.1 $\mu g\ kg^{-1}\ min^{-1}$ remifentanil for the remaining 15 min in addition to the propofol. At the end of 30 min the study period ended. Further propofol was given as appropriate and the anaesthetic technique chosen for the operation started.

Sedation scores were assessed every 5 min immediately before arterial pressure measurement and venous blood sampling. This was performed by the same research anaesthetist for the whole study to minimize inter-observer variability. We used the responsiveness part of the Observer Assessment of the Alertness/Sedation Scale (OAAS) [1] This scale assesses responses to verbal and mild tactile stimulus (5, alert; 4, responds to normal tone voice; 3, responds to loud voice; 2, does not respond to voice but responds to mild prodding; 1, does not respond to prodding).

Blood was taken from a cannula in the arm contralateral to

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

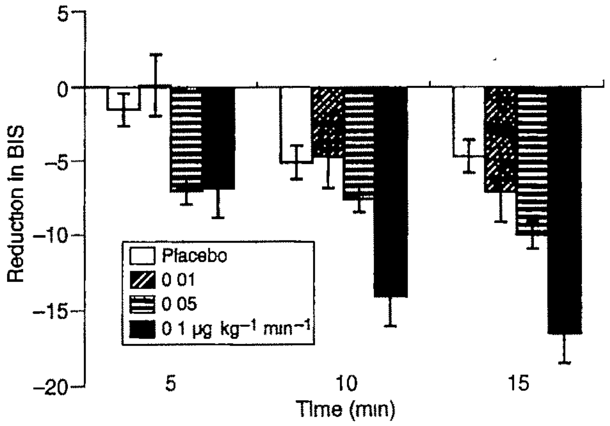


Fig 1 Mean reduction in bispectral index score (with SEM) after the addition of the four remifentanil infusion doses (placebo, 0.01, 0.05, 0.1 μg kg^{-1} min^{-1} remifentanil). After 15 min there is a strong correlation between remifentanil and reduction in BIS (Spearman's rank correlation r=0.415, P<0.01)

the infusion for measurements of propofol blood concentration at 10, 20 and 30 min and analysed using high-pressure liquid chromatography. A C18 3u ODS 10 cm × 4.6 mm column was used with fluorimetric detection (Kratos 980 fluorescence detector). Duplicate assays were required to be within 20% of each other and a mean of the two was taken as the result.

The BISs were downloaded every 5 s to a palm-top computer. Subsequently a BIS was calculated every 5 min by taking the average of the previous 30 s of data.

From previous work we calculated that we required eight patients in each group to have an 80% chance of detecting a difference in mean BIS of 10 at the end of the study period with a significance level of 0.05. Thus 10 patients were recruited to each of the four groups. Results were analysed with SPSS v.7.5.1 for Windows using analysis of variance, c^2 test, t-test and Spearman's rank correlation where appropriate.

There was no significant difference in measured propofol concentrations between the four groups. The haemodynamic variables remained stable for all patients in the four groups and had no statistical (ANOVA P<0.05) or clinically significant differences. The respiratory rate was significantly lower in the 0.1 μg kg^{-1} min^{-1} group at 20, 25 and 30 min than in the other groups (P<0.01). Indeed four patients in this group became apnoeic and required chin lift and hand ventilation. This additional stimulation may have caused some arousal and thus raised the BIS in these patients.

After 15 min there was no significant difference between the BIS scores of the placebo, 0.01, 0.05 or 0.1 μg kg^{-1} min^{-1} (mean BIS scores 74.1, 82.8, 75.1 and 71.6, respectively). The BIS for each patient at this time was then used as the baseline. The reduction in BIS after the introduction of the randomized dose of remifentanil was calculated for each patient (Fig. 1). We found a greater reduction in BIS with increasing doses of remifentanil. There was a significant correlation between the dose of remifentanil and the change of BIS after 15 min of infusion (Spearman's rank correlation r=0.415; P<0.01)

We also observed that when all the sedation scores were compared with their corresponding BIS scores for all the patients in the study, a significant correlation was found. (Spearman's rank correlation r=0.768; P<0.01).

Comment

We have shown that BIS was reduced by increasing infusion rates of remifentanil and that there was a strong correlation between BIS and sedation with this combination of drugs. The Spearman's rank correlation obtained (0.768) for the correlation of BIS with sedation is similar to that found for propofol alone in other studies (0.744[3], 0.883[1]).

Previous studies using an opiate with a hypnotic agent either showed no effect on BIS or found that it made interpretation more complicated.[5] The primary aims of the studies were not to show the sedation properties of opiates and used non-sedating dosages. Iselin-Chaves and colleagues used alfentanil 100 ng ml^{-1} with propofol.[6] Glass and colleagues found that alfentanil 300 ng ml^{-1} did not induce unconsciousness.[1] Most of the studies used varying doses of hypnotics[4] with primary aims differing from those of this study, confounding the interpretation of the effect of the opiate. In our study the greater remifentanil infusion doses caused clinically deeper levels of sedation, reflected in the lower BIS. At 15 min we clearly saw a dose-related effect of remifentanil upon BIS.

The combination of propofol 2 μg ml^{-1} target-controlled infusion with remifentanil produced sedation for this group of patients with few problems when using 0.01 or 0.05 μg kg^{-1} min^{-1} remifentanil. With 0.1 μg kg^{-1} min^{-1} remifentanil there was apnoea, indicating that this dose was too great. Remifentanil, with its short half-life and cardiovascular stability, may have advantages over propofol alone for adjusting levels of sedation.

In summary we have shown that increasing doses of remifentanil infusion cause a greater reduction in BIS and suggest that opiates reduce BIS when combined with propofol.

References

1 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997, **86**: 836–47

2 Liu J, Singh H, White PF. Electroencephalogram bispectral analysis predicts the depth of midazolam-induced sedation. *Anesthesiology* 1996; **84**. 64–9

3 Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997; **84**: 185–9

4 Sebel PS, Lang E, Rampil IJ, White PF A multicenter study of bispectral electroencephalogram analysis for monitoring anaesthetic effect. *Anesth Analg* 1997; **84**: 891–9

5 Vernon JM, Lang E, Sebel PS, Manberg P. Prediction of movement using bispectral electroencepalograhic analysis during propofol/alfentanil and isoflurane/alfentanil anesthesia. *Anesth Analg* 1995; **80**: 780–5

6 Iselin-Chaves IA, Flaishon R, Sebel PS, *et al.* The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998, **87**: 949–55

British Journal of Anaesthesia **84** (4): 491–3 (2000)

Role of dominant hand position during external cardiac compression

P. Kundra*, S. Dey and M. Ravishankar

Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry 605 006, India

**Corresponding author*

Nineteen previously trained resident anaesthetists were instructed to perform adult single-rescuer basic life support for 5 min on a manikin, in a double-blind crossover design, changing the hand of contact with the sternum from right to left while performing external cardiac compression (ECC). Total, correct and incorrect ECCs comprising of inadequate depth, wrong hand placement, incomplete relaxation and too much compression were recorded and grouped according to the dominant hand (group DH) or non-dominant hand (group NH) in contact with the sternum. The number of correct ECCs was significantly greater in group DH, median 141 compared to group NH, median 97; $P<0.005$. More ECCs were of inadequate depth in group NH, median 34 as compared to a median of 8 in group DH; $P<0.005$. Similarly, the incidence of wrong hand placement was significantly higher in group NH; median of 4 versus median of 0 in group DH, $P<0.05$. The incidence of incomplete relaxation and too much ECC was not significantly different between the two groups ($P>0.05$). We conclude that ECC is performed with fewer errors when the dominant hand of the rescuer is placed in contact with the sternum.

Br J Anaesth 2000; **84**: 491–3

Keywords: cardiopulmonary resuscitation, basic life support, external cardiac compression

Accepted for publication: November 8, 1999

Modern cardiopulmonary resuscitation (CPR) can be traced to 1960 with the reintroduction of mouth to mouth ventilation and the description by Kouwenhoven and co-workers[1] of the effectiveness of closed chest massage. External cardiac compression (ECC) remains the standard method to enhance circulation and survival after cardiac arrest. The skill of ECC is best learnt and optimized on manikins. Despite extensive teaching and training of rescuers using manikins, the vast majority of patients admitted with out-of-hospital cardiac arrest die prior to hospital discharge.[2] Multiple factors contribute to these grim statistics. A major factor has been the inability of medical staff to perform adequate CPR as confirmed by a previous study.[3] This study on a manikin was designed to evaluate whether the position of the rescuer's dominant hand in relation to the non-dominant hand (above or below) has any influence on the effectiveness of external cardiac compression and to evaluate the skill retention 1 month after training.

Methods and results

Nineteen resident anaesthetists were selected to participate in the study. All of them had undergone comprehensive training and assessment during a programme conducted by the Department of Anaesthesiology and Critical Care, Jawaharlal Institute of Postgraduate Medical Education and Research on CPR teaching and training 1 month previously. No prior warning was given and candidates were requested not to discuss the study with their colleagues.

The study was conducted in a double-blind, crossover design. The subjects were randomly selected to perform adult single-rescuer basic life support manoeuvres on a manikin for 5 min as per the 1998 European Resuscitation Council (ERC) guidelines.[4] Each subject was presented with the scenario of a witnessed collapse of an adult in the hospital foyer. The situation was simulated using a Laerdal Skillmeter Resusci Anne. All the subjects performed ECC with the right hand placed in contact with the sternum on the first occasion and with the left hand in contact with the sternum on the second occasion. The crossover of the subjects was within 1 week of the first occasion. Metronome beep facility provided in the manikin was used as a guide to maintain a constant compression rate of 100 min^{-1}. Variables recorded during ECC performance were total number of ECCs, number of correct compressions, too much compression, inadequate

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

compression, incomplete relaxation of the chest, and wrong hand placement. Data were recorded and evaluated from the skillmeter screen display by an observer blinded to the study groups. After completing the ECC on the second occasion, each subject was instructed to indicate his dominant hand status in a sealed envelope. The envelopes were opened on completion of the study and the data were grouped as group DH, where the subject's dominant hand was in contact with the sternum, with the non-dominant hand on top; and group NH, where the same subject's non-dominant hand was in contact with the sternum with the dominant hand on top. The data were analysed using the Wilcoxon sign rank test for paired observations. A value of $P<0.05$ was considered significant.

A total number of 19 anaesthesia residents participated in the study. All of them except one were right handed. When asked at the end of the study, 15 residents failed to recollect which hand was kept below in direct contact with the sternum during training in CPR, while four of them remembered that their dominant hand was placed below.

The groups were comparable with regard to total number of ECC and the rate at which it was performed; $P>0.05$. The number of correct ECC in group DH was significantly greater, median 141 (126–153) compared to group NH, median 97 (60–140); $P<0.005$.

Evaluation of incorrectly performed ECC revealed that a significantly greater number of ECC fell short of the required depth, median 34 (15–99) in group NH compared to a median of 8 (5–13) in group DH; $P<0.005$ (Fig. 1). Similarly, in group NH, the hand was placed at the wrong site during performing compression significantly more often, median 4 (0–12), than in group DH, median 0 (0–1); $P<0.05$ (Fig. 1). The incidence of ECC exceeding the recommended depth and with incomplete relaxation was not significantly different between the two groups; $P>0.05$ (Fig. 1).

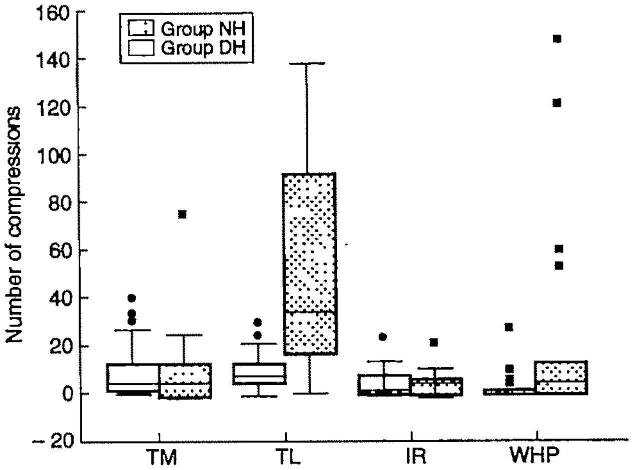


Fig 1 Box and whisker plot illustrating the details of incorrect external cardiac compression performed by 19 subjects using the non-dominant hand (group NH), or the dominant hand (group DH) in contact with the manikin. ● Represents outliers more than 1.5 times the interquartile range in the two groups, and ■ represents extremes more than three times the interquartile range in the two groups. TM, too much compression, TL, too little compression; IR, inadequate relaxation, WHP, wrong hand placement.

Comment

Rudikoff and co-workers[5] suggested that conventional CPR provides only 25–30% of normal cerebral perfusion. The inherent inefficiency in CPR, possibly coupled with the inability of the medical staff to perform adequate CPR,[3] contributes to the poor outcome in the majority of cardiac arrest victims.[2] Our study suggests that positioning the dominant hand in contact with the sternum can lead to a significant change in the magnitude of the force applied upon the sternum in the manikin.

Functional differences between the two cerebral hemispheres are related to hemispheric specialization and handedness. Thus, skilful, sequential–analytical hand functions are learnt spontaneously by instinct with the dominant hand. In most individuals with left hemisphere dominance the right hand is used preferentially for writing and other practical skills.[6] ECC is a specialized skill, where the hand which is in direct contact with the sternum is perhaps responsible for the direction in which the force is applied. As the dominant hand is more effective in directing the force at right angles to the sternum, the majority of the subjects were able to perform ECC more accurately in group DH. Moreover, with the non-dominant hand below, the subjects were less likely to limit contact with the sternum to the heel of their hand, resulting in dissipation of the force from other parts of the hand. Further, the applied force was misdirected resulting in significantly increased incidence of wrong hand placement and inadequate depth during ECC in group NH. In fact, in one subject, all the 140 compressions were of wrong hand placement in spite of identifying the hand placement area 10 times during change over from ventilation to compression. The subject had no wrong hand placement while using the dominant hand.

A laboratory study[7] suggests that rate of compression has an important bearing on the compression duration and force which should be kept constant during manual CPR. The metronome beep facility provided in the manikin helped to keep the ECC rate constant at 100 min^{-1}. This facility was used to optimize the performance so as to keep one variable constant and comparable.

A study by Bell and co-workers[3] reported that only eight out of 30 trained anaesthetists (27%) performed more than 70% of ECCs effectively. On the contrary, subjects in our study showed adequate CPR skills, possibly because they were trained in CPR 1 month previously and were made aware of the 1998 ERC guidelines as a part of the protocol before undertaking the study.

We conclude that the dominant hand should be in contact with the sternum, with the non-dominant hand on top, while performing ECC. This should be emphasized during training and should be considered for inclusion in future guidelines on CPR.

References

1 Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed chest cardiac massage. *JAMA* 1960; **173**: 1064–7

2 Eisenberg MS, Horwood BT, Cummins RO, Reynolds-Harette R, Hearne TR. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med* 1990; **19**: 179–86

3 Bell JH, Harrison DA, Carr B. Resuscitation skills of trainee anaesthetists. *Anaesthesia* 1995; **50**: 692–4

4 The 1998 European Resuscitation Council guidelines for adult single rescuer basic life support. *Resuscitation* 1998; **37**: 67–80

5 Rudikoff MT, Maughan WL, Freund P, Weisfeldt ML. Mechanisms of blood flow during cardiopulmonary resuscitation. *Circulation* 1980; **61**: 345–52

6 Carpenter RHS. Analysis and storage of information by cerebral cortex. In: Hobsley M, Saunders KB, Fitzsimons JT, eds. *Neurophysiology*. London: Edward Arnold, 1990; 314–8

7 Weisfeldt ML, Halperin HR. Cardiopulmonary resuscitation: beyond cardiac massage. *Circulation* 1986; **74**: 443–8

British Journal of Anaesthesia **84** (4): 494–6 (2000)

Epidural top-up solutions for emergency Caesarean section: a comparison of preparation times†

D. N. Lucas, P. J. Borra and S. M. Yentis*

Magill Department of Anaesthesia, Intensive Care and Pain Management, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK

**Corresponding author*

We compared the preparation times of three solutions commonly used for epidural top-up for emergency Caesarean section. Twenty-two anaesthetists were asked to prepare fresh solutions in random order as quickly as possible: 0.5% bupivacaine 20 ml (B); 2% lidocaine 20 ml with 1:200 000 epinephrine (LE); and 0.5% bupivacaine 10 ml and 2% lidocaine 10 ml with 1:200 000 epinephrine and 8.4% sodium bicarbonate 2 ml (BLEB). Preparation times for B were approximately half of those for LE, which in turn were approximately half of those for BLEB ($P=0.0001$). If local anaesthetic solutions with additives such as epinephrine or bicarbonate are prepared just before emergency Caesarean section, any possible reduction in onset time that they might afford may be offset by the additional preparation time required.

Br J Anaesth 2000; **84**: 494–6

Keywords: anaesthetic techniques, epidural

Accepted for publication: December 8, 1999

Epidural analgesia in labour may be extended for emergency Caesarean section with a variety of solutions. We have recently demonstrated that there is no difference in the time taken for the sensory block to reach T4 when labour epidural analgesia is extended for emergency Caesarean section with either 0.5% bupivacaine, 2% lidocaine with 1:200 000 epinephrine, or a 50:50 mixture of 0.5% bupivacaine and 2% lidocaine with 1:200 000 epinephrine.[1] It has been suggested that the addition of sodium bicarbonate may improve the speed of onset of local anaesthetic solutions in the epidural space.[2] Because of concerns about the instability of previously mixed preparations of local anaesthetic and additives such as epinephrine and bicarbonate,[3] these solutions are usually made up immediately before use. There is therefore the potential for delay while such solutions are prepared.

The aim of this study was to compare the preparation times of three commonly used epidural top-up solutions: 0.5% bupivacaine 20 ml (B); 2% lidocaine 20 ml with 1:200 000 epinephrine (LE); and 0.5% bupivacaine 10 ml and 2% lidocaine 10 ml with 1:200 000 epinephrine and 8.4% sodium bicarbonate 2 ml (BLEB).

Methods and results

The solutions were presented in random order to 22 volunteers from the anaesthetic department. The time taken for anaesthetists to prepare the three solutions was recorded, starting from when the first syringe packet was opened to when the study solution was ready in a 20 ml syringe. The solutions were presented for preparation in the standard form that they appear at our hospital:

B: two 10 ml plastic ampoules of 0.5% bupivacaine;

LE: one 20 ml ampoule of 2% lidocaine plus a 1 ml ampoule of 1:1000 epinephrine (0.1 ml to be added to lidocaine 20 ml using a 1 ml syringe);

BLEB: one 10 ml ampoule of 0.5% bupivacaine, one 10 ml ampoule of 2% lidocaine, a 1 ml ampoule of 1:1000 epinephrine and a 50 ml Minijet® syringe containing preservative-free 8.4% bicarbonate (2 ml to be added to the 20 ml solution).

Subjects were also provided with 20 ml, 2 ml and 1 ml syringes and 21 G hypodermic needles. Data were analysed using the Friedman statistic for repeated measures; $P<0.05$ was taken as significant.

Twenty-two anaesthetists participated: eight consultants, 10 specialist registrars and four senior house officers. Preparation times for B were less than those for LE, which in turn were less than those for BLEB ($P=0.0001$; Fig. 1).

---

†Presented at the European Society of Obstetric Anaesthesiologists 6th Congress, Dublin, 1999.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

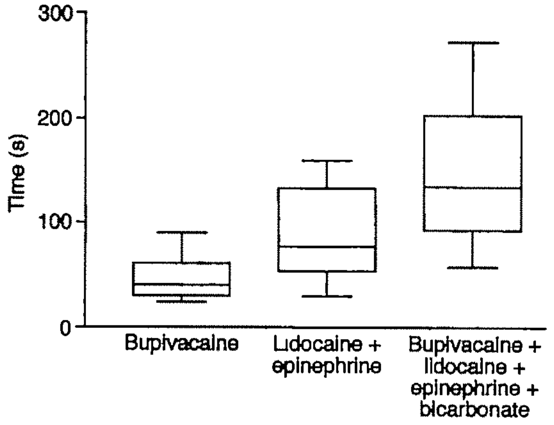


Fig 1 Preparation times for 0.5% bupivacaine 20 ml; 2% lidocaine 20 ml with 1:1000 epinephrine 0.1 ml; and a mixture of 0.5% bupivacaine 10 ml, 2% lidocaine 10 ml, 1:1000 epinephrine 0.1 ml and 8.4% bicarbonate 2 ml. The range (whiskers), interquartile range (box) and median (horizontal bar) are shown

Comment

We found that addition of epinephrine alone or epinephrine and sodium bicarbonate to local anaesthetic solutions increased the time taken to prepare the mixture.

Although carbonated local anaesthetic solutions have been advocated for reducing epidural onset times, the evidence supporting this is conflicting.[4] Furthermore, the additional preparation time we have demonstrated could offset any potential benefit. The BLEB mixture has been found to have mean onset times for sensory blockade to T4 of 13.1[2] and 12.7[5] min when used for epidural anaesthesia for *elective* Caesarean section. However, this mixture has not been studied for extending labour epidural analgesia for *emergency* Caesarean section and its potential to reduce onset time in this scenario is unknown. We have recently compared 0.5% bupivacaine, 2% lidocaine with epinephrine and a bupivacaine–lidocaine–epinephrine mixture for extending low-dose epidural analgesia for emergency Caesarean section, and found median onset times for sensory blockade to T4 of 14, 10 and 12 min respectively.[1] These differences were not statistically significant. In the absence of direct comparisons for emergency Caesarean section, we cannot estimate what the benefit of the BLEB mixture might be, but suggest it is likely to be no more than a few minutes. Given that its preparation may delay topping-up an epidural by up to 4 min, we believe more evidence is needed before BLEB is recommended for extending epidural analgesia for emergency Caesarean section.

Differences in preparation time may not always be clinically significant since not all emergency Caesarean sections are true 'emergencies'. However, in a truly urgent case such differences can be important. Spinal or general anaesthetics are alternative techniques; however, in the presence of a functioning epidural, a spinal block represents a second invasive procedure and also risks causing an excessively high block.[6] The problems of emergency general anaesthesia in the parturient are well established.

With the exception of the Minijet® syringe, clinically available bicarbonate solutions contain preservatives. The Minijet® syringe contains 50 ml of sodium bicarbonate; to use this routinely has implications with regard to cost, or sterility if the same syringe is used repeatedly.

We did not address if preparation times might have improved with practice and our numbers were too small to permit analysis between different grades of anaesthetist. The majority of volunteers who took part in our study regularly work on the labour ward and all except one had more than 1 yr of training in anaesthesia.

The more complex the mixture, the greater the potential for errors during preparation, especially when in a hurry. Uncertainty over any clinical advantage of the BLEB mixture, the requirement for four separate drugs and the potential for error are reasons why this solution is not used in our unit. Other hazards of mixing solutions include the possibility of bacterial contamination and drug incompatibility; for example adding bicarbonate 2 ml to 0.5% bupivacaine 20 ml causes instant precipitation.[4] Another consideration is the variation possible when mixing very small quantities of drugs, the final concentration being affected by the deadspace of the instrument used for aspiration and the presence of air bubbles in very small volumes of injectate.[7]

While preparation and onset times are important considerations when assessing an epidural top-up solution, the quality of analgesia provided is also important. Fernando and colleagues demonstrated improved analgesia when bicarbonate was added to epidural solutions for elective Caesarean section.[5] Whether this also applies to emergency Caesarean section would need examination in a randomized controlled trial.

In conclusion, we have demonstrated that addition of sodium bicarbonate or epinephrine to local anaesthetic to extend epidural analgesia for emergency Caesarean section increases the preparation time. In view of this and the other potential problems of additives, it would seem prudent to consider using simple solutions only, until good evidence is provided for the benefits of these additives.

Acknowledgement

DNL was supported by an Obstetric Anaesthetists' Association Research Fellowship

References

1 Lucas DN, Ciccone GK, Yentis SM. Extending low-dose epidural analgesia for emergency Caesarean section – a comparison of three solutions. *Anaesthesia* 1999; **54**: 1173–7

2 Patel M, Craig R, Laishley R. A comparison between epidural anaesthesia using alkalinised solution and spinal (combined spinal/

epidural) anaesthesia for elective caesarean section. *Int J Obstet Anesth* 1996; **5**: 236–9

3 Robinson J, Sun Wai WYS, Fernando R. Chemical stability of bupivacaine, lidocaine and epinephrine in pH adjusted solutions. *Anesthesiology* 1999; **90**: A86

4 Morison DH. Alkalinization of local anaesthetics. *Can J Anaesth* 1995; **42**: 1076–9

5 Fernando R, Jones HM. Comparison of plain and alkalinized local anaesthetic mixtures of lignocaine and bupivacaine for elective extradural caesarean section. *Br J Anaesth* 1991; **67**: 699–703

6 Beck GN, Griffiths AG. Failed extradural anaesthesia for Caesarean section. Complication of subsequent spinal block. *Anaesthesia* 1992; **47**: 690–2

7 Dull RO, Peterfreund RA. Variations in the composition of spinal anesthetic solutions: the effects of drug addition order and preparation methods. *Anesth Analg* 1999; **87**: 1326–30

British Journal of Anaesthesia 84 (4): 497–9 (2000)

In vitro validation of gastric air tonometry using perfluorocarbon FC 43 and 0.9% sodium chloride

J. Graf[1], B. Königs[1], K. Mottaghy[2] and U. Janssens[1]*

[1]Medical Clinic I and [2]Institute of Physiology, University Hospital of RWTH Aachen, Pauwelsstrasse 30, D-52057 Aachen, Germany

**Corresponding author: Klinikum der RWTH Aachen, Medizinische Klinik I, Pauwelsstrasse 30, D-52057 Aachen, Germany*

Monitoring splanchnic perfusion by means of gastric intramucosal tonometry is carried out using saline, or more recently, air tonometry using the Tonocap. The objective of this study was the validation of the Tonocap in saline and perfluorocarbon FC 43. The two methods underestimated the predefined $P\text{CO}_2$ value by an average of 10%, with clinically acceptable precision. Accuracy of the Tonocap improved at high $P\text{CO}_2$ values (9.33 and 9.94 kPa), whereas saline tonometry was superior at low $P\text{CO}_2$ values (3.99 and 3.75 kPa). The Tonocap provides a fast and reliable estimation of the $P\text{CO}_2$, and with the revised software requiring only 10 min of equilibration, will increase the comparability of future studies.

Br J Anaesth 2000: **84**: 497–9

Keywords: equipment; gastrointestinal tract; measurement techniques, tonometry; monitoring

Accepted for publication: October 22, 1999

Two methods of monitoring splanchnic perfusion and oxygenation by means of gastric tonometry are available at present: conventional saline tonometry and, more recently, the Tonocap. In contrast to saline tonometry, the Tonocap automatically inflates a balloon with air and the catheter is constantly connected to the monitor, resulting in a closed system. This new device is expected to solve at least some of the practical and methodological problems inherent in saline tonometry.[1] Since the software for the Tonocap has been revised recently and now allows an equilibration time of only 10 min, a new *in vitro* validation study was essential. This *in vitro* study was designed to validate the accuracy of the Tonocap using two liquids: sodium chloride 0.9% and perfluorocarbon FC 43 (PFC 43).

Methods and results

Four tonometry catheters (TRIP Tonometry Catheter, 16 F; Tonometrics Instrumentarium Corporation, Datex Ohmeda Division, Helsinki, Finland) were placed in a sealed container serving as an equilibration chamber. Two tonometers were connected to the Tonocap monitors (Tonocap TC 200, version 2.1, 1998; Tonometrics Instrumentarium Corporation). Conventional saline tonometry was carried out with the two remaining catheters. Details of the two methods have been published elsewhere.[2] The container was partly filled with PFC 43 (3M Specialty Chemical Division, Neuss, Germany), which is known for its exceptionally high carbon dioxide solubility, or sodium chloride 0.9%. Steady-state $P\text{CO}_2$ was reached by constantly bubbling carbon dioxide test gases (4 and 9.97% carbon dioxide in nitrogen, relative accuracy ±1%; Linde, Cologne, Germany), and the temperature was maintained at 37°C. The $P\text{CO}_2$ (kPa) used as the reference for tonometry was calculated from the carbon dioxide content of the calibration gas, the vapour pressures of saline 0.9% (6.27 kPa) and PFC 43 (0.24 kPa) at 37°C and the barometric pressure (P_{bar}; median 99.98 kPa, range 99.80–100.20 kPa) according to Dalton's law:

$$P\text{CO}_2 = \%\text{CO}_2 \times (P_{\text{bar}} - \text{vapour pressure}) \times 100.$$

Throughout all experiments the chamber $P\text{CO}_2$ was checked simultaneously with the Tonocap measurements every 10 min, by (1) sampling 0.5 ml PFC 43 or sodium chloride 0.9% for $P\text{CO}_2$ analysis using a conventional blood-gas analyser (ABL 505; Radiometer Copenhagen, Denmark) and (2) recording the real-time readings of an intravascular carbon dioxide sensor (Paratrend 7; Diametrics Medical, High Wycombe, Buckinghamshire, UK).

All samples were obtained by the same investigator, and no factor was applied to correct for incomplete equilibration. In both PFC 43 and sodium chloride 0.9%, two series of experiments were carried out, one series at a high $P\text{CO}_2$ level and one at a low level.

The statistical analysis was executed using SPSS 7.5 (SPSS, Chicago, IL, USA) and MedCalc 4.16a (F. Schoonjans, Ghent, Belgium). All data are expressed as mean (SD). The paired *t* test was used to compare the different methods at corresponding experimental time-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Bias, precision and 95% confidence interval (95% CI) of the Tonocap and conventional saline tonometry in the estimation of chamber $P\mathrm{co}_2$ in PFC 43 and sodium chloride 0.9% with respect to values calculated according to Dalton's law. Bias=mean difference between Tonocap and conventional saline tonometry; precision=standard deviation of the difference; n=number of paired measurements. *The number of measurements at high $P\mathrm{co}_2$ levels was limited by an empty gas tank; therefore, the number of measurements at low $P\mathrm{co}_2$ was increased. However, a total number of 160 measurements in PFC 43 could not be achieved

		PFC 43 (high, 9.94 kPa; low, 3.99 kPa)				**Sodium chloride 0.9% (high, 9.33 kPa; low, 3.75 kPa)**			
		n	**Bias (%)**	**Precision (%)**	**Mean (95% CI) (kPa)**	***n***	**Bias (%)**	**Precision (%)**	**Mean (95% CI) (kPa)**
Tonocap	All	156	−9.0	4.7	Not applicable	160	−12.2	4.9	Not applicable
	High	64*	−6.6	2.8	9.33 (9.26–9.40)	80	−9.9	4.1	8.45 (8.38–8.52)
	Low	92	−10.9	2.8	3.58 (3.55–3.82)	80	−14.3	5.1	3.25 (3.21–3.29)
Conventional saline tonometry	All	20	−11.4	4.2	Not applicable	20	−11.3	7	Not applicable
	High	8	−15.0	2.1	8.44 (8.41–8.70)	10	−17.5	4.1	7.37 (7.71–8.02)
	Low	12	−8.6	2.5	3.66 (3.60–3.72)	10	−5.3	4.7	3.56 (3.44–3.68)

points. Pearson's correlation coefficient was calculated for all data sets. Bias and precision were analysed according to the method of Bland and Altman.[3]

No significant within-method difference was observed among the means obtained by the two Tonocap monitors and among the two conventional tonometry catheters. Consequently, the results obtained with each method were pooled for further analyses.

Tonocap and saline tonometry underestimated the calculated $P\mathrm{co}_2$ in both sodium chloride 0.9% and PFC 43. At the high $P\mathrm{co}_2$ levels, the bias of the Tonocap was smaller compared with the low $P\mathrm{co}_2$ levels and saline tonometry in both solutions, whereas the accuracy of saline tonometry was higher at the low $P\mathrm{co}_2$ levels and decreased with increasing $P\mathrm{co}_2$. The overall precision of the two methods was similar (Table 1).

Direct comparison of the Tonocap with saline tonometry yielded an overall bias of 2% in PFC 43 and −0.3% in saline (precision 6.7 and 8%, respectively).

Comment

The main finding of this study is that the Tonocap and conventional saline tonometry underestimated the calculated chamber $P\mathrm{co}_2$ by an average of 10%. The precision of both methods was within acceptable clinical limits.

The bias of the Tonocap increased with decreasing $P\mathrm{co}_2$ level. This might be attributed in part to the Tonocap's display, which allows only one decimal place; values between 3.5 and 3.6 kPa, for example, are rounded. This may lead to an absolute difference between the measured and the displayed value of 0.04 kPa, corresponding to approximately 1% bias at low $P\mathrm{co}_2$ levels but only 0.5% bias at high $P\mathrm{co}_2$ levels in this study. However, this does not explain the observed difference of more than 4%.

The deviation of saline tonometry from the calculated $P\mathrm{co}_2$ at high chamber $P\mathrm{co}_2$ levels was probably caused by constructional features of the blood-gas analyser itself and the low stability of carbon dioxide in saline. This results in loss of carbon dioxide before the sample reaches the measuring electrode. Because the $P\mathrm{co}_2$ gradient is the determinant of carbon dioxide diffusion, this environmental loss of carbon dioxide is pronounced at high $P\mathrm{co}_2$ values.[4]

Creteur and colleagues used a conventional blood-gas analyser to assess the $P\mathrm{co}_2$ of an equilibration chamber. At a given $P\mathrm{co}_2$ level of 10.66 kPa, they found a smaller bias (−2.1%) and better precision (2.4%) compared with our results (mean of six measurements, 10 min dwell time, values from the original publication converted into kPa and percentages).[5]

The majority of studies validating the Tonocap calculated the chamber $P\mathrm{co}_2$ according to Dalton's law. Kolkman and colleagues calculated the mean of 20 repeated measurements with an equilibration time of 5 min at four $P\mathrm{co}_2$ levels, and reported a bias of −2% and a precision of 2% with a response time of 19 (2) min (i.e. time to detect 95% of an instantaneous change in bath $P\mathrm{co}_2$).[6] The 5-min cycle time used in this study was carried out with a prototype Tonocap system that was not available commercially. Temmesfeld-Wollbrück and colleagues repeated their measurements three times and found no bias at a chamber $P\mathrm{co}_2$ of 5.33 kPa and a bias of 3.58%, with a precision of 1.54% at 7.60 kPa (data from the original publication converted into kPa).[7]

Using the capnograph facility of the Tonocap as a reference, Barry and colleagues reported a bias of −2.5% and a precision of 2.1%.[8] This procedure potentially avoids possible sources of error, such as the analysis of $P\mathrm{co}_2$ with a conventional blood-gas analyser. However, dependent variables must not be correlated with each other, and validation of the sensor without an independent reference method might introduce systematic errors.

A major drawback is that different reference methods and study procedures (with regard to dwell time, $P\mathrm{co}_2$ level and the number of repeated measurements) limit the comparability of studies. Furthermore, the revised software of the Tonocap used in this study did not allow us to adjust the cycle time to confirm previous results.

In conclusion, the Tonocap is an easy, fast and precise device for estimating intramucosal $P\mathrm{co}_2$ within clinically acceptable limits. Moreover, the new software provides the first standardized method for the bedside assessment of perfusion and oxygenation in the critically ill patient.

References

1 Sato Y, Weil MH, Tang W. Tissue hypercarbic acidosis as a marker of acute circulatory failure (shock). *Chest* 1998; **114**: 263–74

2 Janssens U, Graf J, Koch KC, Hanrath P. Gastric tonometry: *in vivo* comparison of saline and air tonometry in patients with cardiogenic shock. *Br J Anaesth* 1998; **81**: 676–80

3 Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986, **1**: 307–10

4 Kolkman JJ, Zwarekant LJ, Boshuizen K, Groeneveld AB, Steverink PJ, Meuwissen SG. Type of solution and $P\text{CO}_2$ measurement errors during tonometry. *Intensive Care Med* 1997, **23**: 658–63

5 Creteur J, DeBacker D, Vincent J-L. Monitoring gastric mucosal carbon dioxide pressure using gas tonometry. *Anesthesiology* 1997; **87**: 504–10

6 Kolkman JJ, Zwaarekant LJ, Boshuizen K, Groeneveld AB, Meuwissen SG. In vitro evaluation of intragastric $P\text{CO}_2$ measurement by air tonometry. *J Clin Monit* 1997, **13**: 115–9

7 Temmesfeld-Wollbruck B, Szalay A, Olschewski H, Grimminger F, Seeger W. Advantage of buffered solutions or automated capnometry in air-filled balloons for use in gastric tonometry. *Intensive Care Med* 1997; **23**: 423–7

8 Barry B, Mallick A, Hartley G, Rodenham A, Vucevic M. Comparison of air tonometry with gastric tonometry using saline and other equilibrating fluids: an in vivo and in vitro study. *Intensive Care Med* 1998; **24**: 777–84

British Journal of Anaesthesia 84 (4): 500–4 (2000)

BJA

CASE REPORTS

Malignant hyperthermia in infancy and identification of novel RYR1 mutation

D. Chamley, N. A. Pollock[1]*, K. M. Stowell[2] and R. L. Brown[2]

Department of Anaesthesia, Middlemore Hospital, Auckland, New Zealand. [1]Department of Anaesthesia, Palmerston North Hospital, Palmerston North, New Zealand. [2]Institute of Molecular BioSciences, Massey University, Palmerston North, New Zealand

**Corresponding author*

Malignant hyperthermia (MH) has been reported as non-existent in children less than 1 yr old, although several unconfirmed reports have been published. A case report of MH in a 6-month-old child is presented, with confirmation of MH susceptibility by *in vitro* contracture testing of quadriceps muscle at 13 yr old. Genetic analysis revealed a novel RYR1 mutation that substitutes arginine 2452 for tryptophan in a region of the calcium channel mutated in several other MH pedigrees.

Br J Anaesth 2000; **84:** 500–4

Keywords: genetic factors, hyperthermia; metabolism, hyperthermia

Accepted for publication. November 8, 1999

Malignant hyperthermia (MH) is an inherited hypermetabolic disorder of skeletal muscle triggered by depolarizing muscle relaxants and potent inhalation anaesthetic agents. The incidence has recently been reported as 1:50 000 anaesthetics administered in adults and 1:15 000 in children.[1] MH in infancy is considered rare[2] or even non-existent.[3] There have been several reports indicating MH reactions in infants[4–8] (Allen, personal communication), but confirmation by *in vitro* contracture testing (IVCT) was not demonstrated in the proband or in immediate relatives. A case report of an MH reaction in a 6-month-old child is presented, and also evidence of a novel RYR1 mutation associated with MH in this family.

Case report

A 6-month-old male born at term (in 1984) following an uneventful pregnancy presented for repair of complete cleft of the right primary and secondary palate, and incomplete cleft of the left primary palate. A first stage repair using a modified Manchester technique was planned. There was no family or medical history of note, he weighed 7.4 kg and physical examination was normal, other than his congenital cleft palate.

He was premedicated with atropine 0.2 mg and droperidol 1 mg orally 90 min before induction. An uneventful gaseous induction of anaesthesia was carried out using halothane, and the trachea was intubated with a size 4.0 Oxford tube. The child breathed spontaneously a mixture of halothane, oxygen and nitrous oxide through a humidified T piece circuit, and was monitored using an ECG, digital plethysmograph, precordial stethoscope and rectal temperature probe (capnography, agent analysis and pulse oximetry were not in general use at this time). Fluids were given through a 24-gauge cannula in the foot, and the patient was well draped to prevent heat loss.

Anaesthesia was uneventful for the first 90 min with a heart rate (HR) of between 155 and 165, temperature increasing from the initial recording of 36.4°C to 37.3°C. Over the following 20 min his temperature increased to 38.5°C. During this time malignant hyperthermia was considered, but the diagnosis initially rejected as it was not known to occur in this age group. During the last 10 min of the case (110–120 min from the start) HR increased from 160 to 190, and his temperature continued to increase, reaching 39°C. At the end of the procedure (120 min from the start) the surgeon noted unexpected masseter muscle rigidity when removing the mouth gag, and on removing the drapes the patient was noted to be very flushed and sweaty. Anaesthetic agents were discontinued, respiration was thought to be adequate, the trachea was extubated and the child taken to recovery where his temperature was found to be 39.5°C. Tachypnoea was then noted, blood-gas analysis showed a pH of 7.195, P_{CO_2} 3.8 kPa, P_{O_2} 13.4 kPa

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

with a base deficit of 13.4 mmol litre^{-1} and a diagnosis of malignant hyperthermia was made. Dantrolene 15 mg (2 mg kg^{-1}) was administered, cooling was commenced using a fan over a wet sheet, and an arterial line and urinary catheter inserted. Sodium bicarbonate, 7.5 mmol was given. Serum potassium was measured at 5.6 mmol litre^{-1}. The maximum temperature reached was 39.5°C 20 min after diagnosis, and 140 min following induction. The temperature returned to normal 80 min after diagnosis, 200 min from the start. No myoglobin was present in the urine and creatine kinase (CK) was initially 290 i.u., rising to 1845 i.u. (normal 0–300 i.u.) 2 h post-anaesthetic. No further therapy was required and an uneventful recovery followed.

Investigation of the family at the time using CK showed his mother to have an elevated level of 623 i.u., while father's and siblings' CK were normal. The CK of the patient measured several months after the reaction was 243 i.u.

At 13 yr old the patient underwent lateral quadriceps muscle biopsy. The test was performed in accordance with the European MH Group protocol.[9] This demonstrated a strongly positive contracture (MHS) to both halothane and caffeine (6.4 g tension to 2% halothane and 5.1 g tension to caffeine 2 mmol litre^{-1} – $n<0.2$ g tension). The mother of the patient had a 4.3 g response to 2% halothane and a 3.7 g response to caffeine 2 mmol litre^{-1}, and was also diagnosed MHS. Histology of the muscle was normal. There was no evidence of myositis or recognizable dystrophy.

The proband was screened for published MH RYR1 mutations in the central mutation region of the ryanodine receptor (RYR1) gene by PCR-amplification of cDNA and automatic sequencing. None of the nine published mutations[10–15] in this region was detected. However, a novel C7354T nucleotide transition that substitutes arginine 2452 for tryptophan was identified. The mother of the proband was also positive for the Arg2452Trp mutation. The mutation was present in the DNA of one of two siblings examined, but these individuals are yet to be examined by IVCT. Segregation of the Arg2452Trp mutation in this small family (family 1) is shown in Figure 1A.

The method of 'single stranded conformational polymorphism analysis' (SSCP)[16] was used to screen for the Arg2452Trp mutation in exon 46 amplified from genomic DNA (Fig. 2). The mutation was not found in 100 normal chromosomes indicating that it is not likely to be a common polymorphism. DNA samples from MHS probands from other NZ MH families were also screened for the mutation by SSCP analysis

The Arg2452Trp mutation was not detected in the DNA from 33 MHS probands examined. However, a new conformational variant was detected in exon 46 in one unrelated MHS patient as shown in Fig. 2. Sequence analysis of this second variant revealed a G7361A mutation that changes arginine 2454 to histidine. This second mutation was identified in an unrelated young male who developed a fulminant MH reaction with masseter muscle spasm, significant hypercapnia, tachycardia and rhabdomyolysis during an emergency orthopaedic procedure. IVCT was strongly positive. The mother of this patient had a normal IVCT (MHN), and both mother and sister were negative with respect to the mutation. The results of a screen for the Arg2454Trp mutation in members of family 2 are presented in Figure 1B.

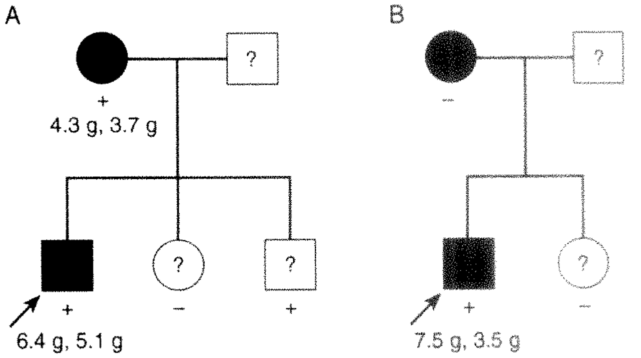


Fig 1 (A) Segregation of the Arg2452Trp mutation in family 1. The presence (+) or absence (–) of the mutant allele is indicated. The proband suffered a MH crisis in infancy and is indicated by an arrow. Filled symbols represent MHS subjects diagnosed by IVCT. IVCT contracture responses (g) of MHS muscle to 2% halothane and caffeine 2 mM, respectively, are shown. (B) Detection of the Arg2454His mutation in a single individual from family 2. Symbols are as described for (A).

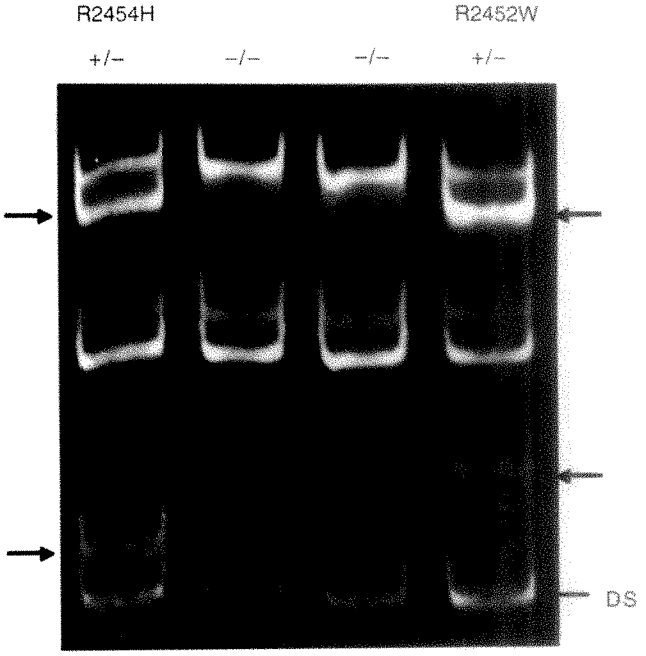


Fig 2 Detection of the R2454H (lane 1) and R2452W (lane 4) mutations in DNA of MH probands by SSCP. Mutations are revealed by the differential mobility of single stranded DNA on 8% non-denaturing polyacrylamide gels, stained with ethidium bromide. Arrows mark mutation-specific SSCP bands that are absent from normal controls (lanes 2 and 3). DS, double-stranded DNA.

Discussion

Pyrexia, increasing tachycardia, rigidity, tachypnoea, and significant metabolic acidosis as well as flushing and sweating provided clinical evidence for MH in this child. The MH clinical grading scale[17] ranks the likelihood that an adverse anaesthetic event represents MH. Points are assigned to abnormal signs and laboratory findings (clinical indicators), the points are then summed to produce a raw score which is translated to a qualitative MH rank indicating with which likelihood MH could occur – from 1 (almost never) to 6 (almost certain). This infant ranked 6 on this clinical grading scale. Confirmation of an MH reaction was demonstrated by positive IVCT, the only reliable screening test for MH susceptibility.[18]

Jaw rigidity was first noted by the surgeon. The anaesthetist at the time (DC) was not aware of rigidity in other muscle groups. In the course of an MH reaction rigidity of the jaw usually presents as masseter muscle spasm at induction of anaesthesia following the use of suxamethonium. In patients not given suxamethonium, muscles of the chest, abdomen and extremities may be involved initially, although eventually rigidity may be generalized.[19] Isolated jaw rigidity in the absence of suxamethonium, 120 min after induction, may represent an alternative presentation of MH in an infant.

Management of the reaction proceeded with few problems. Dantrolene was administered in a dose of 2 mg kg^{-1} which is lower than the recommended starting dose of 2.4 mg kg^{-1}.[20] Lerman found normal metabolism of dantrolene in young children and a dose of 2.4 mg kg^{-1} produces safe and predictable blood concentrations. Reconstituted dantrolene, pH 9–10, is irritant to veins and in an infant should be injected into a fast-running intravenous infusion or large central vein.[21] Intraosseous administration provides an alternative route if venous access is problematic.

Reactions in infants younger than 6 months have not been previously proven. There have been several reports of MH reactions in the newborn associated with the stress of labour, but alternative aetiologies for these reactions could be proposed.[21–23] At our institution MH suspect newborn are monitored for 4 h with pulse, ventilatory frequency and temperature, and no significant abnormalities have been reported in 66 infants born to MHS or mothers related to MHS individuals (Langton, unpublished observations). Reactions associated with farrowing have not been reported in susceptible piglets. There may in fact be resistance to the development of MH in the neonatal period and early infancy. Fay and Gallant[24] found that MHS piglets had delayed reactions when exposed to triggering agents, and *in vitro* responses were not as pronounced as the contractures usually observed in muscle from older MHS pigs. These findings were confirmed by Wedel.[2]

As indicated earlier, several case reports in infants younger than 6 months have been published in the anaesthetic literature, but with the exception of Faust and co-workers,[25] IVCT was not performed. In this latter case triggering agents were not administered, the reaction ranked 3 or 'somewhat less than likely' on the MH clinical grading scale and IVCT was performed from sterno-mastoid muscle and not quadriceps, and therefore the diagnosis could be questioned.

IVCT in this case was undertaken in early teenage years, and in general we follow the policy of Ellis and co-workers[9] who established a lower age limit of 10 yr due to inconsistency in muscle responses in young children, possibly related to immature muscle tissue. The size of the muscle sample to be removed and scarring are other considerations. However, Gronert[26] has found normal contracture responses in small numbers of children and other units will test younger children.[27] If the proband is less than 10 yr old, some units will test the parents and if they are normal the child is considered normal.[9 28] However, in our unit there has been parental resistance to this procedure and a reaction could also result from a *de novo* mutation in the proband.

The primary event triggering MH is the abnormal release of calcium from the sarcoplasmic reticulum (SR) that initiates sustained contractile and metabolic activity in skeletal muscle.[29] The SR calcium release channel was identified as the ryanodine receptor, a large tetramer, observed as the 'foot' structure spanning the junctional SR and surface membranes.[30] Abnormalities in the regulation of calcium release from the ryanodine receptor were revealed in studies of skeletal muscle from MHS pigs and humans.[31] In 1990, McCarthy and co-workers[32] identified the ryanodine receptor gene (RYR1) as a likely candidate for the MHS locus, and in the subsequent 9 yr the role of RYR1 has been confirmed with the discovery of numerous RYR1 mutations in MH families.[13] The Arg2452Trp mutation described in this report takes the number of published MH/central core disease mutations in the RYR1 gene to 20. RYR1 mutations may underlie only 50% of cases of MH susceptibility,[33] and defects in any number of proteins involved in myoplasmic calcium homeostasis may be commonly expressed as the MH syndrome. In fact, genetic heterogeneity in MH is now firmly established with the description of five additional MH loci on chromosomes 17q, 7q, 3q, 1q and 5p.[34–38] The emerging complexity of MH genetics excludes the development of a general genetic test to replace the IVCT in the near future. There are several reports of MHS diagnoses in individuals who are negative for a particular mutation segregating in their family[11 39–41] suggestive of either false positive IVCT or the occurrence of additional MH genes. Consequently, genetic testing cannot safely replace the IVCT to establish MHN status.

We have searched for the published mutations in the central RYR1 region by automatic sequencing of complementary DNA (cDNA), using skeletal muscle tissue excised for IVCT. RNA was extracted from frozen muscle tissue and used as a template to synthesize the cDNA. Because the cDNA comprises only the coding region of a gene, this approach allows efficient simultaneous screening for clustered RYR1 mutations, as well as enabling detection of any novel mutations. A novel arginine 2452 to tryptophan RYR1 mutation was identified in this patient. The mutation was also detected in the proband's mother, who tested MHS, and a sibling who is still too young to undergo IVCT examination. The MH status of the father has not yet been examined by IVCT. An investigation of the co-segregation of the mutation with the MH disorder was restricted by the small number of patients investigated by IVCT in this family. Therefore, it is possible that the mutation represents a polymorphism that is not causative of MH. However, the mutation is highly unlikely to be a coincidental polymorphism as it was not detected in the normal population.

While screening the DNA of unrelated MHS probands for the novel Arg2452Trp mutation, a second mutation that changes arginine 2454 to histidine was found in an unrelated adult MHS proband. The Arg2454His substitution identified in this second proband (family 2) occurs only 2 amino acids downstream of the Arg2452Trp mutation that was identified in the first proband (family 1). The Arg2454His mutation was recently described in an Italian family.[15] The independent identification of the same mutation in an unrelated NZ proband supports a causative role for the Arg2454His substitution in MH.

The two arginine substitutions detected in this study (Arg2452Trp and Arg2454His) occur in close proximity to two previously described MH mutations at the arginine 2458 residue.[14] The clustering of four MH mutations within a 7 amino acid region, and the conservation of the three affected arginine residues across species in all RYR1, RYR2 and RYR3 sequences[14 15] implies a critical regulatory role for the positively charged amino acids in this domain of the ryanodine receptor. Interestingly, nine out of 11 mutations reported in the central region of the ryanodine receptor involve arginine residues.

Acknowledgements

We thank Ms Danielle James for technical assistance The genetic analysis was supported in part by grants from the New Zealand Lotteries Grants Board, The Palmerston North Medical Research Foundation, and the Australian and New Zealand College of Anaesthetists

References

1 Abraham RB, Adnet P, Glauber V, Perel A. Malignant hyperthermia. *Postgrad Med J* 1998; **74**: 11–7

2 Wedel DJ. The effect of age on the development of MH in susceptible piglets. *Anesthesiology* 1994; **81**: A426

3 Bennett EJ, Bowyer DE. Thomas CC, ed. *Principles of Paediatric Anaesthesia*. Illinois· Springfield, 1982; 66–71

4 Wiswell TE, Bent RC, Solenberger R. Malignant hyperthermia in infancy. *South Med J* 1989; **82**: 1451–2

5 Bailey AG, Bloch EC. Malignant hyperthermia in a three-month-old American Indian infant. *Anesth Analg* 1987, **66**: 1043–5

6 Wilhoit RD, Brown Jr RE, Bauman LA. Possible malignant hyperthermia in a 7-week-old infant [see comments]. *Anesth Analg* 1989; **68**: 688–91

7 Pennington GP, Joeris L. Malignant hyperthermia in a 3-month-old infant: a case report. *J Med Assoc Ga* 1996; **85**: 162–3

8 Meluch AM, Sibert KS, Bloch EC Malignant hyperthermia following isoflurane anesthesia in an American Lumbee Indian. *N C Med J* 1989; **50**. 485–7

9 Ellis FR, Halsall PJ, Harriman DG. The work of the Leeds Malignant Hyperpyrexia Unit, 1971–84. *Anaesthesia* 1986; **41**: 809–15

10 Zhang Y, Chen HS, Khanna VK, De Leon S, Phillips MS, Schappert K, *et al* A mutation in the human ryanodine receptor gene associated with central core disease. *Nature Genet* 1993, **5**. 46–50

11 Phillips MS, Khanna VK, De Leon S, Frodis W, Britt BA, MacLennan DH. The substitution of Arg for Gly2433 in the human skeletal muscle ryanodine receptor is associated with malignant hyperthermia. *Hum Mol Genet* 1994; **3**. 2181–6

12 Keating KE, Quane KA, Manning BM, Lehane M, Hartung E, Censier K, *et al*. Detection of a novel RYR1 mutation in four malignant hyperthermia pedigrees. *Hum Mol Genet* 1994; **3**. 1855–8

13 Manning BM, Quane KA, Ording H, Urwyler A, Tegazzin V, Lehane M, *et al*. Identification of novel mutations in the ryanodine-receptor gene (RYR1) in malignant hyperthermia genotype-phenotype correlation. *Am J Hum Genet* 1998; **62**: 599–609

14 Manning BM, Quane KA, Lynch PJ, Urwyler A, Tegazzin V, Krivosic-Horber R, *et al*. Novel mutations at a CpG dinucleotide in the ryanodine receptor in malignant hyperthermia. *Hum Mutat* 1998; **11**· 45–50

15 Barone V, Massa O, Intravaia E, Bracco A, Di Martino A, Tegazzin V, *et al*. Mutation screening of the RYR1 gene and identification of two novel mutations in Italian malignant hyperthermia families. *J Med Genet* 1999; **36**: 115–8

16 Hongyo T, Buzard GS, Calvert RJ, Weghorst CM. 'Cold SSCP': a simple, rapid and non-radioactive method for optimized single-strand conformation polymorphism analyses. *Nucleic Acids Res* 1993; **21**· 3637–42

17 Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, *et al* A clinical grading scale to predict malignant hyperthermia susceptibility *Anesthesiology* 1994; **80**. 771–9

18 Ellis FR. Malignant hyperthermia. how important after 30 years. *Acta Anaesthesiol Belg* 1990; **41**: 61–3

19 Britt BA. The clinical aspects of malignant hyperthermia. In. Nalda Felipe MA, Gottman S, Khambatta HJ, eds. *Malignant Hyperthermia Current Concepts*. Bad Homburg: Normed, 1988

20 Lerman J, McLeod ME, Strong HA. Pharmacokinetics of intravenous dantrolene in children. *Anesthesiology* 1989, **70** 625–9

21 Ward A, Chaffman MO, Sorkin EM Dantrolene. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **32**· 130–68

22 Sewall K, Flowerdew RM, Bromberger P Severe muscular rigidity at birth: malignant hyperthermia syndrome? *Can Anaesth Soc J* 1980; **27**: 279–82

23 Cupryn JP, Kennedy A, Byrick RJ. Malignant hyperthermia in pregnancy. *Am J Obstet Gynecol* 1984; **150**: 327–8

24 Fay RS, Gallant EM. Halothane sensitivity of young pigs *in vivo* and *in vitro*. *Am J Physiol* 1990, **259**: R133–8

25 Faust DK, Gergis SD, Sokoll MD. Management of suspected malignant hyperpyrexia in an infant. *Anesth Analg* 1979, **58** 33–5

26 Gronert GA. Contracture responses and energy stores in quadriceps muscle from humans age 7–82 years. *Hum Biol* 1980; **52**: 43–51

27 Allen G, Rosenberg H. Diagnosis of malignant hyperthermia in infants [letter, comment]. *Anesth Analg* 1990; **70**: 115–6

28 Ording H, Ranklev E, Fletcher R. Investigation of malignant hyperthermia in Denmark and Sweden. *Br J Anaesth* 1984; **56**. 1183–90

29 MacLennan DH, Phillips MS. Malignant hyperthermia. *Science* 1992; **256**: 789–94

30 Lai FA, Erickson H, Block BA, Meissner G. Evidence for a junctional feet-ryanodine receptor complex from sarcoplasmic reticulum. *Biochem Biophys Res Commun* 1987; **143**: 704–9

31 Mickelson JR, Louis CF. Malignant hyperthermia: excitation-contraction coupling, Ca^{2+} release channel, and cell Ca^{2+} regulation defects. *Physiol Rev* 1996; **76**: 537–92

32 McCarthy TV, Healy JM, Heffron JJ, Lehane M, Deufel T, Lehmann-Horn F, *et al.* Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12-13.2. *Nature* 1990; **343**: 562–4

33 Ball SP, Johnson KJ. The genetics of malignant hyperthermia. *J Med Genet* 1993; **30**: 89–93

34 Levitt RC, Olckers A, Meyers S, Fletcher JE, Rosenberg H, Isaacs H, *et al.* Evidence for the localization of a malignant hyperthermia susceptibility locus (MHS2) to human chromosome 17q. *Genomics* 1992; **14**: 562–6

35 Iles DE, Lehmann-Horn F, Scherer SW, Tsui LC, Olde Weghuis D, Suijkerbuijk RF, *et al.* Localization of the gene encoding the alpha 2/delta-subunits of the L- type voltage-dependent calcium channel to chromosome 7q and analysis of the segregation of flanking markers in malignant hyperthermia susceptible families. *Hum Mol Genet* 1994; **3**: 969–75

36 Sudbrak R, Procaccio V, Klausnitzer M, Curran JL, Monsieurs K, van Broeckhoven C, *et al.* Mapping of a further malignant hyperthermia susceptibility locus to chromosome 3q13.1. *Am J Hum Genet* 1995; **56**: 684–91

37 Robinson RL, Monnier N, Wolz W, Jung M, Reis A, Nuernberg G, *et al.* A genome wide search for susceptibility loci in three European malignant hyperthermia pedigrees. *Hum Mol Genet* 1997; **6**: 953–61

38 Monnier N, Procaccio V, Stieglitz P, Lunardi J. Malignant-hyperthermia susceptibility is associated with a mutation of the alpha 1-subunit of the human dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor in skeletal muscle [see comments]. *Am J Hum Genet* 1997; **60**: 1316–25

39 Adeokun AM, West SP, Ellis FR, Halsall PJ, Hopkins PM, Foroughmand AM, *et al.* The G1021A substitution in the RYR1 gene does not cosegregate with malignant hyperthermia susceptibility in a British pedigree. *Am J Hum Genet* 1997; **60**: 833–41

40 Serfas KD, Bose D, Patel L, Wrogemann K, Phillips MS, MacLennan DH, *et al.* Comparison of the segregation of the RYR1 C1840T mutation with segregation of the caffeine/halothane contracture test results for malignant hyperthermia susceptibility in a large Manitoba Mennonite family [see comments]. *Anesthesiology* 1996; **84**: 322–9

41 Fagerlund TH, Ording H, Bendixen D, Islander G, Ranklev Twetman E, Berg K. Discordance between malignant hyperthermia susceptibility and RYR1 mutation C1840T in two Scandinavian MH families exhibiting this mutation. *Clin Genet* 1997; **52**: 416–21

British Journal of Anaesthesia 84 (4): 505–7 (2000)

Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment

A. Patel, E. Harrison, A. Durward* and I. A. Murdoch

Department of Paediatric Intensive Care, Guy's Hospital, St Thomas Street, London SE1 9RT, UK
**Corresponding author*

Recombinant human deoxyribonuclease (rhDNase) is a mucolytic agent used to relieve peripheral airway obstruction in patients with cystic fibrosis. We report dramatic sustained improvement following the intratracheal administration of rhDNase to a 3-yr-old boy with acute life-threatening asthma in whom 48 h of aggressive therapy had failed.

Br J Anaesth 2000; **84**: 505–7

Keywords: complications, asthma; children; enzymes, recombinant human deoxyribonuclease

Accepted for publication: November 1, 1999

Cystic fibrosis is characterized by chronic airway inflammation caused by infection of thick secretions. The increased viscosity of these secretions is caused by a large content of extracellular deoxyribonucleic acid (DNA), from the migration and death of neutrophils associated with the inflammatory process.[1] By altering sputum from a thick viscous gel to a flowing liquid, recombinant human DNase (rhDNase) can relieve peripheral airway obstruction and improve respiratory symptoms and lung function in patients with cystic fibrosis.[2] In severe asthma, airflow obstruction that does not respond to bronchodilators may be caused by occlusion of the airways by mucous plugs and inflammatory exudate. Elevated sputum DNA levels have been reported in patients with acute asthma (with or without infection),[3] so rhDNase may be effective as a mucolytic agent in the treatment of patients with acute asthma. We describe dramatic sustained improvement in airflow obstruction following the intratracheal administration of rhDNase in a child with acute life-threatening asthma that did not respond to conventional treatment.

Case report

A 3-yr-old 15-kg boy with six previous hospital admissions for asthma presented to his local hospital with a 24-h history of wheeze and coryzal symptoms. His regular medications were inhaled budesonide 400 µg and terbutaline twice daily. At the local hospital he failed to respond to treatment with nebulized salbutamol 2.5 mg hourly, hydrocortisone 60 mg i.v. 6-hourly and infusions of aminophylline 1 mg kg^{-1} h^{-1} and salbutamol 1 µg kg^{-1} min^{-1} i.v. The patient deteriorated and after 9 h had respiratory arrest, followed by tracheal intubation and mechanical ventilation. Arterial blood gas analysis after intubation showed pH 7.10, Pa_{CO_2} 12.0 kPa, Pa_{O_2} 12.3 kPa and base excess – 4.0 mmol $litre^{-1}$ with manual ventilation, and FI_{O_2} of 1.0. He was transferred to the regional paediatric intensive care unit, where mechanical ventilation was difficult and respiratory acidosis persisted. The chest radiograph revealed marked hyperinflation without segmental atelectasis. The blood leukocyte count was 24.3 × 10^9 $litre^{-1}$ (neutrophils 22.4 × 10^9 $litre^{-1}$) and *Streptococcus pneumonii* sensitive to all antibiotics was cultured from the bronchoalveolar lavage performed on admission. He was treated with cefuroxime 300 mg i.v. 8-hourly. The patient was sedated with morphine 40 µg kg^{-1} h^{-1} and muscle relaxation was achieved with vecuronium 100 µg kg^{-1} h^{-1}. A lung protective strategy using a Servo 900C ventilator with permissive hypercapnia was adopted. Peak airway pressure was limited to 46 cm H_2O, with tidal volume from 76 ml (5.1 ml kg^{-1}) to 97 ml (6 4 ml kg^{-1}) and a ventilation rate from 10 to 14 breath min^{-1} At these settings, the severity of the airway obstruction was evident from a marked decrease in inspiratory pause pressure to 17–21 cm H_2O. Over the subsequent 24 h, although oxygenation was adequate (Pa_{O_2} 8.2–15.6 kPa, FI_{O_2} 0.6–0.8), the respiratory acidosis persisted (pH 7.04–7.16, Pa_{CO_2} 10.6–17.5 kPa). Salbutamol therapy was increased to 6 µg kg^{-1} min^{-1}, ketamine infusion was started at 30 µg kg^{-1} min^{-1} i.v., and magnesium sulphate 1 g given i.v. to achieve bronchodilation, but this was unsuccessful. General anaesthesia using isoflurane for bronchodilation also failed to relieve airflow obstruction. The expired concentration of isoflurane was maintained at 1%, monitored via a connection from the DATEX AS/3™ gas analyser placed between the Y connector and endotracheal tube.

With no improvement in ventilation after 48 h of this therapy and physiotherapy with saline lavage (0.9% saline 5 ml), we decided to give intratracheal rhDNase in an attempt to reverse the airflow obstruction.

RhDNase 2.5 mg was dissolved in 0.9% saline 10 ml and

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

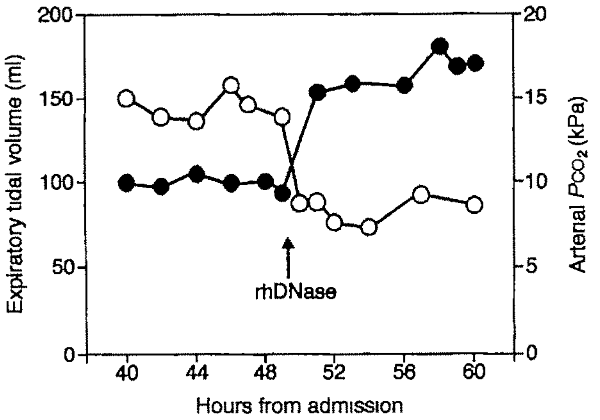


Fig 1 Expiratory tidal volume (closed circles) and arterial P_{CO_2} (open circles) against time from admission.

half of this volume (5 ml) was given via an 8F feeding catheter into the trachea with the patient placed in the right lateral position. Manual ventilation was carried out during the procedure, the peak airway pressure not exceeding 45 cm H_2O. After 15 min of manual ventilation and vigorous physiotherapy, the procedure was repeated with the patient in the left lateral position. Tracheal suction was performed after 30 min and clear loose secretions were removed. Within 30 min a dramatic, sustained improvement in ventilation occurred, allowing a reduction in the peak airway pressure from 44 to less than 26 cm H_2O with a corresponding increase in expired tidal volume from 93 to 196 ml (Fig. 1). The arterial blood gas improved, with an increase in pH from 7.17 to 7.41 and a decrease in P_{CO_2} from 13.8 to 7.6 kPa within 3 h of the procedure. This improvement was sustained; the tracheal tube was removed 72 h after rhDNase therapy and the patient made an uneventful recovery.

Discussion

In acute severe asthma, airflow obstruction is caused by bronchospasm, airway inflammation and mucous plugging.[4 5] Conventional treatment aims to decrease bronchospasm with bronchodilator therapy and airway inflammation with steroid therapy, and provide supportive care with mechanical ventilation. In most patients conventional treatment is effective, although a small number of patients may fail to improve, deteriorate and eventually die from asphyxia due to severe airflow obstruction.[5] Post mortem examinations of patients who have died from severe asthma have shown widespread severe mucous plugging of the airways.[6]

This patient failed to respond to conventional treatment with bronchodilator therapy with i.v. salbutamol, corticosteroids, magnesium sulphate, ketamine and isoflurane. Following the use of the mucolytic agent rhDNase, a dramatic sustained improvement was observed in ventilation, with resolution of the respiratory acidosis. This improvement appeared to be directly related to the intratracheal administration of rhDNase and not simply the result of the vigorous physiotherapy that had been performed at regular intervals without effect. Sudden responsiveness to bronchodilator therapy would be unusual after 48 h of maximum medical treatment that included steroids. Manual alveolar recruitment is also unlikely to explain the improvement because the airway pressures used during the instillation of rhDNase were similar to those used during conventional mechanical ventilation.

A role for mucolytic therapy in refractory status asthmaticus has been suggested, with the use of the mucolytic agent acetylcysteine.[4] However, this is irritant and can aggravate bronchospasm, making its use in a patient with severe ventilatory difficulties questionable. Nebulized rhDNase has also been proposed as a mucolytic in non-intubated asthmatic patients with lobar atelectasis.[7] Direct administration of rhDNase by bronchoscopy into regions of mucous plugging has been reported in intubated, mechanically ventilated asthmatic patients.[8 9] In both of these cases lobar atelectasis cleared completely within hours of administration. In the absence of clinical or radiological evidence of segmental atelectasis, bronchoscopy was not attempted in our patient. Bronchoscopy can help in the management of refractory status asthmaticus with mucous plugging, although its efficacy in diffuse small airway mucous plugging is unknown.[4]

In contrast to all previous reports,[7–9] this case, to our knowledge, is the first to describe an improvement in airflow obstruction in the absence of lobar atelectasis. This may be of importance in those asthmatic patients who do not respond to conventional treatment because of unrecognized diffuse small airway mucous plugging. The proposed mechanism of action of rhDNase in acute asthma is a reduction in the viscoelastic properties of mucous plugs, by the hydrolysis of extracellular DNA derived from degenerating leucocytes and epithelial debris.[9] Other factors that may also be important include the alteration of mucous clearance mechanisms by enhanced ciliary function and the mobilization of secretions.[10] We found rhDNase to be well tolerated and without side-effects, as have previous reports,[7–9] although dose-dependent mucosal airway damage with haemoptysis due to increased airway protease activity may occur.[1 11]

Despite advances in the medical management of acute asthma and improved ventilatory strategies, a small number of patients still develop life-threatening airflow obstruction refractory to therapy. In such patients the potential benefits and apparent safety of rhDNase may be preferred to other options, such as extracorporeal membrane oxygenation.

In summary, we describe dramatic reversal of airflow obstruction following the intratracheal administration of rhDNase in a ventilated child with refractory status asthmaticus.

References

1 Ramsey B, Dorkin HL. Consensus Conference: Practical applications of pulmozyme. *Paediatr Pulmonol* 1994; **17**: 404–8
2 Geddes DM, Shah PL. Where are we now with rhDNase? *Lancet* 1999; **353**: 1727

3 Fahy JV, Liu J, Wong H, Boushey HA. Cellular and biochemical analysis of induced sputum from asthmatic and healthy patients. *Am Rev Resp Dis* 1993; **147**: 1126–31

4 Henke CA, Hertz M, Gustafson P Combined bronchoscopy and mucolytic therapy for patients with severe refractory status asthmaticus on mechanical ventilation· a case report and review of the literature. *Crit Care Med* 1994; **22**:1880–3

5 Benatar SR Fatal asthma. *N Engl J Med* 1986; **314**· 423–9

6 Hogg JC. Varieties of airway narrowing in severe and fatal asthma *J Allergy Clin Immunol* 1987; **80**: 417–9

7 Puterman AS, Weinberg EG rhDNase in acute asthma. *Paediatr Pulmonol* 1997; **23**: 316–31

8 Greally P. Human recombinant DNase for mucous plugging in status asthmaticus. *Lancet* 1995; **346**: 1423–4

9 Durward A, Forte V, Shemie S Resolution of mucous plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000; **27**· 560–2

10 Puchelle E, Zahm JM, de Bentzman S, Grosskopf C, Shak S, Mongel D, Pohn JM. Effects of rhDNase on purulent airway secretions in chronic bronchitis. *Eur Respir J* 1996; **9**. 765–6

11 Rochat T, Pastore FD, Schlegel-Hauter SE, Filthuth I, Auckenthaler R, Bell D, Suter S. Aerosolized rhDNase in cystic fibrosis· Effect on leucocyte proteases in sputum. *Eur Respir J* 1996; **9**· 2200–20

British Journal of Anaesthesia 84 (4) 508–9 (2000)

Monitoring equipment induced tachycardia in patients with minute ventilation rate-responsive pacemakers

P. A. Southorn*, G. S. Kamath, G. M. Vasdev and D. L. Hayes[1]

Department of Anesthesiology and Division of Cardiovascular Diseases and [1]Department of Internal Medicine, Mayo Clinic, Rochester, MN 55905, USA

**Corresponding author*

Minute ventilation-sensing pacemakers enable the paced heart to respond to an increased workload. Two patients with such a pacemaker developed pacemaker-driven tachycardia when connected to an electrocardiogram (ECG) monitor also capable of documenting ventilatory frequency and ECG lead disconnection. This tachycardia stopped when the ECG leads were removed. These pacemakers and monitors emit a low-amplitude electrical current and measure the resultant impedence signal across the chest. When patients are connected to the monitor the pacemaker sensor summates both impedence signals and the paced heart rate is increased as a result.

Br J Anaesth 2000; **84:** 508–9

Keywords: equipment, pacemakers; heart, arrhythmia, tachycardia; monitoring, ventilation

Accepted for publication: October 20, 1999

With their ability to vary the heart rate with changes in minute ventilation, minute ventilation rate-responsive pacemakers enable the paced heart to mimic the normal cardiac response to increased workload.[1] To date this has been one of the most successful physiological sensors in enabling the cardiac output to be increased proportionally with workload. These pacemakers have been documented to improve patient exercise tolerance and well-being. Minute ventilation is calculated by detecting changes in transthoracic impedence derived from low-amplitude electrical pulses from the pacemaker. Such impedence plethysmography is also used to enable display of the patient's ventilatory frequency and detect disconnection of the eletrocardiogram (ECG) by monitors used in the operating suite and intensive care unit. Recently we encountered two patients; both of whom had a specific type of minute ventilation rate-responsive pacemaker who developed inappropriate paced heart rate increases when connected to such a monitor used in our operating room recovery unit. This communication describes what happened and discusses the appropriate management of patients fitted with such pacemakers.

Case reports

The first patient, a 73-yr-old man, had a Telectronics Meta 1254 minute ventilation rate-responsive pacemaker implanted 5 yr previously after complete heart block developed following radiofrequency ablation for chronic atrial fibrillation. In the operating room he underwent uneventful dental extraction under general anaesthesia comprising a propofol induction and anaesthetic maintenance with sevofluorane, nitrous oxide and oxygen, and minimal amounts of fentanyl.

The second patient was a 77-yr-old man who was implanted with the same brand of pacemaker for complete heart block secondary to ischaemic heart disease. To evaluate a possible recurrence of his prostate cancer he underwent a transrectal needle biopsy of the prostate and cystoscopy under sedation using fentanyl, midazolam and propofol.

Our cardiac monitors in the operating rooms do not use impedence plethysmography, and both patient's heart rates were pacemaker controlled at 60–70 beats per min during the procedures. The Hewlett-Packard (Burlington, MA, USA) Omnicare cardiac monitors in our postoperative recovery room do use impedence plethysmography. Immediately upon ECG lead connection to this monitor, both patients' paced heart rate rapidly increased to 120 beats per min. Immediate access to a pacemaker interrogator with the first patient revealed that this upper rate pacing was controllable by altering the pacemaker settings. Disconnection from the monitor resulted in the paced heart rate in both patients decreasing to their baseline rate. Neither patient sustained harm from this transient iatrogenic increase in heart rate (Fig.1).

Discussion

The Telectronics Meta 1254 minute ventilation rate-responsive pacemaker (Telectronics has recently been purchased by St Jude Pacing Company, Sylmar, CA, USA) was

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

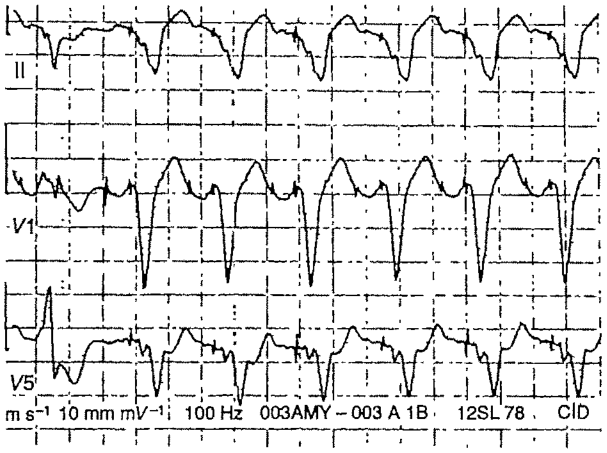


Fig 1 Paced tachycardia (117 beats per min) in our second patient which occurred upon his being connected to a monitor in the recovery suite

the successor of the first minute ventilation rate-adaptive pacemaker marketed. This particular pacemaker has been implanted in significant numbers of patients worldwide. Several other pacemaker companies have, or are contemplating, minute ventilation-sensing pacemakers.

The physiological basis of this pacemaker technology is that the minute ventilation is directly correlated to body oxygen consumption and cardiac output. To measure the patient's minute ventilation, a low-amplitude current pulse is emitted by the pacemaker and the resultant impedence signal across the chest, reflecting tidal volume and ventilatory frequency, is used to calculate minute ventilation. Programming of such pacemakers is relatively simple; the lower pacing rate is programmed with the patient at rest and the maximum pacing rate is based on individual clinical characteristics. This type of pacemaker can, therefore, be adjusted to individual patient requirements for an increased heart rate with a given increased work level.

Monitors used in operating suites and intensive care units (ICU) commonly use similar impedence plethysmography to document the patient's ventilatory frequency and detect ECG lead disconnection. When connected to such a monitor the pacemaker sensor measures the summated impedence signals resulting from the monitor and its own electrical current, falsely interprets the information as an increase in transthoracic impedence and increases the heart rate accordingly. This is what happened to our patients.

Such upper rate pacing could potentially be misinterpreted and treated as, for example, a pathological cardiac rhythm[2] or inadequate anaesthetic depth.[3] In patients with coronary artery disease or when the pacemaker has been inappropriately programmed, the resulting tachycardia could potentially also produce myocardial ischaemia and haemodynamic compromise.[4 5] If this potential is recognized before the patient is connected to such monitors, reprogramming the pacemaker to a non-rate-adaptive pacing mode would avoid inappropriate sensor-driven pacing. When such preventative management has not been used and tachycardia on connection to the monitor does occur, as happened in our patients, the correct treatment is to remove and disconnect the monitor.

This potential problem has been recognized and documented previously,[2–4] and the Federal Drug Administration (FDA) has recently issued an advisory notice to manufacturers of monitoring equipment.[6] We have informed the Medical Devices Agency of the UK Department of Health about our experience. It is important that physicians working with such patients in the operating suite and ICU be familiar with this scenario. These previous reports, like ours, documented the problem with the Telectronics pacemaker, and to date, this has not been reported with similar pacemakers produced by other manufacturers Other devices using electrical impedence plethysmography, such as echocardiography equipment, apnoea monitors and external defibrillators, could potentially exert a similar effect on the function of these pacemakers. Because these pacemakers function by their ability to detect and process voltage changes, they are also vulnerable to other externally produced currents, produced, for example, by electrocautery and radio frequency catheter ablation.[4] Controlled manipulation of the patient's minute ventilation has also been reported to produce unwanted change in heart rate with these pacemakers.[3]

References

1 Mond H, Strathmore N, Kertes P, Hunt D, Baker G Rate responsive pacing using a minute ventilation sensor *PACE* 1988, **11**: 1866–74

2 Wallden J, Gupta A, Carlsen H-O Supraventricular tachycardia induced by Datex patient monitoring system. *Anesth Analg* 1998; **86**: 1339

3 Von Knobelsdorff G, Goering M, Nalgele H, Scholz L Inference of anesthetic management with the pacing rate of rate responsive pacemakers. *Anaesthetist* 1996; **45**: 856–60

4 Chew EW, Troughear RH, Kuchar DL, Thorburn CW. Inappropriate rate changes in minute ventilation rate responsive pacemakers due to interference by cardiac monitors. *PACE* 1997, **20**: 276–82

5 Rozner MA, Nishman RJ. Pacemaker-driven tachycardia revisited. *Anesth Analg* 1999; **88**: 965

6 Office of Surveillance and Biometrics, FDA, Rockville, MD 20850, USA. FDA Post market safety notification. Interaction between minute ventilation rate-adaptive pacemakers and cardiac monitoring and diagnostic equipment Oct. **6**, 1998

British Journal of Anaesthesia **84** (4) 510–3 (2000)

Stunned myocardium after hip arthroplasty

M. Mizogami[1]*, K. Shimo[2], T. Taguchi[3] and Y. Horita[3]

[1]Department of Anaesthesiology, Asahi University, 1851 Hozumi, Hozumi-cho, Motosu-gun, Gifu-ken, 5010296, Japan. [2]Department of Anaesthesia and [3]Department of Cardiology, Keiju Medical Center, 94 Tomioka-cho, Nanao-shi, Ishikawa-ken, 9268605, Japan

**Corresponding author*

We report a case of ST-segment elevation occurring in all leads of the ECG during hip arthroplasty. It is thought that this resulted from a stunned myocardium because wall motion abnormalities were reversible, there was no evidence of fixed or vasospastic coronary occlusion and there was only a slight increase in serial cardiac enzymes. Treatment with nicorandil improved the patient's cardiac function. A $[^{123}I]$MIBG test revealed a high myocardial washout rate, suggesting that the stunned myocardium was caused by exposure to excessive norepinephrine induced by anaesthesia or surgery.

Br J Anaesth 2000; **84**: 510–3

Keywords: heart, myocardial function; complications

Accepted for publication: November 22, 1999

Stunned myocardium is defined as prolonged, yet reversible, post-ischaemic ventricular dysfunction, usually without tissue necrosis.[1] It has been described in animal models, and growing evidence suggests that it is a clinically relevant phenomenon in humans.[2] The mechanism of stunned myocardium is unknown, although several factors, such as oxygen-derived free radicals,[3 4] changes in calcium homeostasis,[5] disruption of cardiac sympathetic neural responsiveness,[6] neutrophil activation–migration[7] or myocardial cell swelling and oedema[8] may be responsible for the prolonged deficit in contractile function. We report an example of myocardial stunning during non-cardiac surgery in a patient on whom we performed a number of cardiac tests to confirm the diagnosis and to guide treatment. We report the findings of single-photon-emission computed tomographs (SPECT) and coronary arteriograms, and discuss the aetiology of stunned myocardium and the efficacy of verapamil or nicorandil in treating it.

Case report

A small, 75-yr-old woman (height 126 cm, weight 26 kg) was scheduled for urgent bipolar hip arthroplasty. Apart from diabetes mellitus, well controlled with insulin (10 units day^{-1}), she had no history of cardiovascular disease. She was anaemic (Hb = 8.9 g dl^{-1}). Physical examination and preoperative 12-lead electrocardiography (ECG) revealed no abnormal findings. Although the patient was diagnosed as having mild mitral regurgitation on transthoracic echocardiography, her left ventricular function was within normal limits. She was not premedicated before surgery. After establishing an intravenous infusion, the patient was connected to a 2-lead ECG (II, V5), pulse oximeter and non-invasive arterial pressure monitor. Following preoxygenation, thiopental 150 mg and vecuronium 6 mg were given intravenously, the trachea was intubated and general anaesthesia was maintained using 1.5–2.0% sevoflurane, nitrous oxide (4 litres min^{-1}) and oxygen (2 litres min^{-1}). After induction, a left radial catheter was inserted for arterial pressure monitoring. The patient's arterial pressure (systolic pressure 130–160 mm Hg) and heart rate (70–80 beats min^{-1}) remained stable during surgery. The operation took 1 h and was uneventful. With the initiation of transtracheal suction after spontaneous breathing had been established, a nodal bigeminy of sudden onset was noted on the ECG monitor. A few seconds later, even though the rhythm had returned to sinus, the monitor revealed ST-segment elevation in leads II and V5. We suspected the patient had suffered an acute myocardial infarction and immediately started i.v. nitroglycerine (1 μg kg^{-1} min^{-1}). A 12-lead ECG revealed a Qs pattern in V1–2 and significant ST-segment elevation in I, II, aVL and V3–6. Approximately 1.5 h after its onset, the patient was transferred to the angiographic room. Left ventriculography (LVG) showed akinesis of the apex and hypokinesis of the anterior and inferior walls. The left ventricular ejection fraction (LVEF) was 27%. Coronary arteriograms revealed no evidence of fixed or vasospastic obstruction in the right or left coronary artery. However, a large area of no reflow phenomenon (slow radio-contrast run-off in the coronary arteriogram) was observed. We considered that thrombotic coronary occlusion had caused the myocardial infarction. After cardiac catheterization, the patient was taken to the intensive care unit (ICU) and given

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

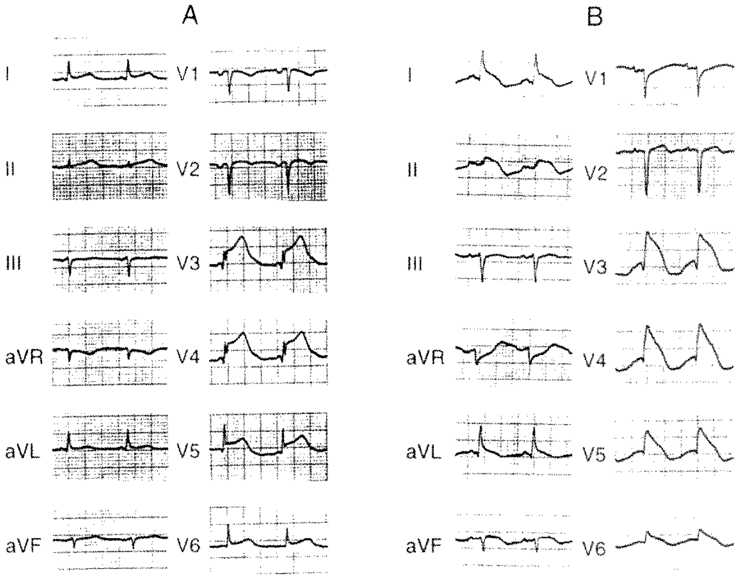


Fig 1 Twelve-lead electrocardiogram recorded at first onset of ST changes in the operating room (A) and during the second episode in the ICU (B).

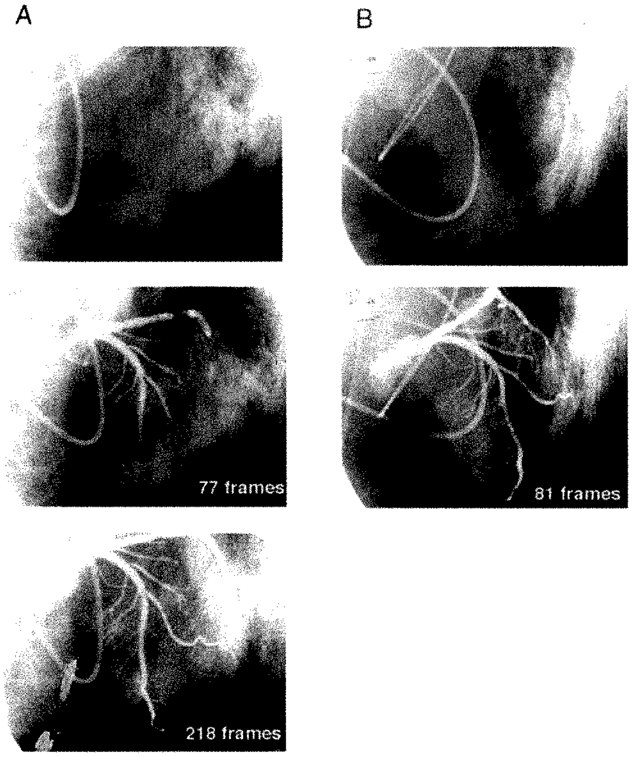


Fig 2 Coronary arteriogram taken before (A) and after (B) the administration of intracoronary verapamil, showing improvement of slow radio-contrast run-off (no reflow phenomenon). There is no evidence of fixed or vasospastic obstruction in the left coronary artery. The description time of the whole left coronary artery is improved from 218 frames to 81 frames by the administration of intracoronary verapamil. 60 frames = 1 s.

continuous i.v. heparin (30 000 units day^{-1}), isosorbide dinitrate (ISDN) (2 μg kg^{-1} min^{-1}) and dopamine (3 μg kg^{-1} min^{-1}). The ST-segment elevation in the precordial leads gradually decreased (Fig. 1).

Two days after the operation, while still in the ICU, the ECG monitor again showed ST-segment elevation. A 12-lead ECG revealed ST-segment elevation in all leads. Repeat emergency cardiac catheterization was performed. The left coronary arteriogram did not show left coronary obstruction, but the no reflow phenomenon was seen, as on the previous day. Verapamil was therefore injected directly into the coronary artery in an attempt to improve distal microvascular dysfunction and intramyocardial microvascular spasm. The no reflow phenomenon in the left coronary artery disappeared immediately. The patient was then treated with continuous i.v. nicorandil (4 mg h^{-1}) to avoid any bradycardia (a frequent side-effect of verapamil and beta-blockers). Serum creatine kinase (CK) increased to 306 units (it is normally <180 units), with an increase of muscle-brain isoenzyme (CK-MB) to 36 units (normally <20 units). Apart from aspiration of gastric contents (day 21 after the operation), the remainder of the patient's ICU stay was uneventful and she was discharged from the ICU 33 days after the operation. LVG revealed improvement of the wall motion abnormality without hypokinesis of the apex and an LVEF of 58% 66 days after the operation (Fig. 2).

With the agreement of the patient's family, SPECT was performed at regular intervals to confirm the diagnosis and determine treatment. Three types of imaging, with thallium-201 chloride (^{201}TlCl), iodine-123 betamethyl-iodophenyl-pentadecanoic acid ([^{123}I]BMIPP) and iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG), gave information about myocardial perfusion, fat metabolism and sympathetic nerve activity respectively. Comparison of the ^{201}TlCl and [^{123}I]BMIPP tomographs taken in the immediate (days 5–15 after operation) and late phases (days 46–53 after operation) of recovery showed complete resolution of the perfusion and fat metabolism defects at the apex. The [^{123}I]MIBG tomographs revealed a high (61%) washout rate (normal = 18–30%/3 h) in the immediate phase over all the left ventricle; damage was limited to the apex in

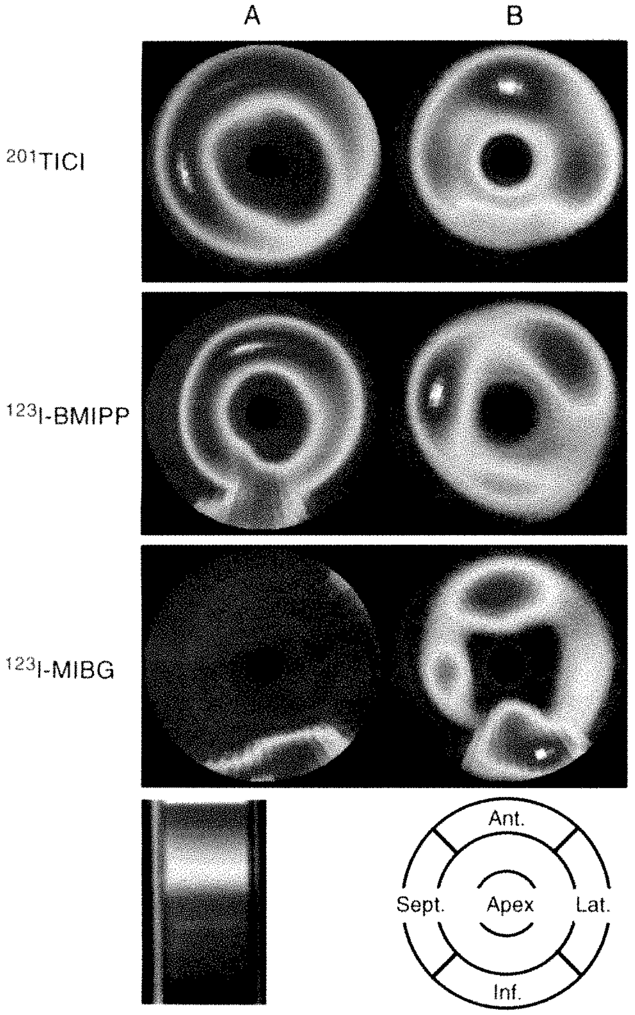


Fig 3 Bull's eye expression of myocardial imaging in the immediate (A) and late (B) phases. Marked defects in the apical area revealed by ^{201}TlCl and [^{123}I]BMIPP were completely restored in the late phase. An increase in sympathetic tone over the left ventricle was observed as a high washout rate (61%) of [^{123}I]MIBG in the immediate phase. Ant., anterior wall; Sept., septum; Lat., lateral wall; Inf., inferior wall.

^{201}TlCl and [^{123}I]BMIPP images. The former finding also improved in the late phase of recovery (Fig. 3).

Discussion

This patient is thought to have suffered a stunned myocardium; the evidence for this is that: wall motion abnormalities were reversible; there was no indication of fixed or vasospastic coronary occlusion; and there was only a slight increase in serial cardiac enzymes despite the severe ST-segment elevation, especially in the second attack.

[^{123}I]MIBG is transported into sympathetic nerve terminals and stored in neuronal vesicles in the same way as norepinephrine, making it possible to investigate sympathetic nerve distribution in the heart *in vivo*.[9,10] The washout rate was calculated as the percent change in cardiac [^{123}I]MIBG activity over time. A higher washout rate indicates increased activity of the myocardial sympathetic nervous system.[11] The changes in ^{201}TlCl and [^{123}I]BMIPP imaging were confined to the apex in the immediate phase, suggesting damaged myocardium in this area in accordance with the findings of the LVG and ECG. In contrast, a high washout rate was observed over the whole of the left ventricle in the immediate phase on [^{123}I]MIBG imaging. If the findings of [^{123}I]MIBG imaging resulted from myocardial damage, ^{201}TlCl and [^{123}I]BMIPP confirmed that it must be limited to the apex of the left ventricle. This increased sympathetic activity could have caused the stunned myocardium rather than resulting from the damage caused by it. We suggest that increased sympathetic tone induced by anaesthesia or by surgical stimulation led to an increase in the release of norepinephrine in the heart. This is also thought to cause neurogenic stunned myocardium in subarachnoid haemorrhage.[12]

The coronary arteriogram of this patient also demonstrated the no reflow phenomenon as the slow run-off of radio-contrast suggested that the blood flow to the stunned area had been markedly reduced, although there was no angiographic evidence of fixed or vasospastic obstruction in the coronary artery. This phenomenon is thought to result from increased microvascular impedance to flow. It has been observed in clinical practice after recanalization of an infarct-related artery by either thrombolysis or balloon angioplasty.[13,14] The term 'no reflow phenomenon' is usually associated with myocardial infarction and occurs secondary to vascular disruption in the local ischaemic area or tissue oedema. Thus it may not be appropriate to apply this term to the wide area of changes in the left ventricle in this case. However, the slow radio-contrast run-off observed would be classified as grade 2 flow according to Thrombolysis in Myocardial Infarction (TIMI) criteria. Grade 2 flow is considered to be compatible with the no reflow phenomenon.[15] Recent studies have suggested that TIMI grade 2 reflow results from microvascular dysfunction in the ischaemic region and may be regarded as reperfusion failure. The underlying mechanisms remain unknown. Piana and colleagues demonstrated that flow-restricting spasm of the distal microvascular bed is responsible.[16] In those studies, the hypothesis of distal spasm as an underlying aetiology is supported by the poor response to nitroglycerine. The distal vessels may lack a sufficient local sulfhydryl pool to convert nitroglycerine to its active nitrosothiol form. Calcium channel antagonists may not be effective because they only act directly on vascular smooth muscle. In our patient, the stunned myocardium was refractory to nitroglycerine and ISDN, although it responded promptly to the administration of intracoronary verapamil. The beneficial effect of beta-blockers, whose cardioprotective properties can be explained by their effects on lipid metabolism and generation of oxygen free radicals, have also been reported in the treatment of this phenomenon.[17,18] However, this patient's severe cardiac dysfunction did not permit us to use beta-blockers or calcium channel antagonists because of the risk of bradycardia developing. Thus we gave a continuous infusion of nicorandil, a nicotinamide nitrate with potassium channel-opening activity, in the ICU. This drug seemed to prevent recurrence of ST-segment elevation and enhanced recovery from the stunned myocardium. Nicorandil is thought to restore myocardial perfusion to the no reflow area by reducing the resistance of the distal microvascular bed by an ATP-sensitive potassium channel-opening effect, the beneficial actions of which on the stunned myocardium are not shared by the nitrovasodilator.[19, 20] These findings suggest that distal microvascular spasm may be the aetiology in this case.

References

1 Braunwald E, Kloner R. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982; **66**: 1146–9

2 Patel B, Kloner RA, Przyklenk K, Braunwald E. Postischemic myocardial 'stunning': a clinically relevant phenomenon. *Ann Int Med* 1988; **108**: 626–8

3 McCold JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985; **312**: 159–63

4 Werns SW, Shea MJ, Lucchesi BR. Free radicals and myocardial injury: pharmacologic implications. *Circulation* 1986; **74**: 1–5

5 Krause S, Hess ML. Characterization of cardiac sarcoplasmic reticulum dysfunction during short-term, normothermic, global ischemia. *Circ Res* 1984; **55**: 176–84

6 Ciuffo AA, Ouyang P, Becker LC, Levin L, Weisfeldt ML. Reduction of sympathetic inotropic response after ischemia in dogs. *J Clin Invest* 1985; **75**: 1504–9

7 Engler R, Covell JW. Granulocytes cause reperfusion ventricular dysfunction after 15-minute ischemia in the dog. *Circ Res* 1987; **61**: 20–8

8 Kloner RA, Ganote CE, Jennings RB. The 'no reflow' phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974; **54**: 1496–508

9 Tobes MC, Jaques S, Jr, Wieland DM, Sisson JC. Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 1985; **26**: 897–907

10 Nakajo M, Shimabukuro K, Yoshimura H *et al.* Iodine-131 metaiodobenzylguanidine intra- and extravesicular accumulation in the rat heart. *J Nucl Med* 1986; **27**: 84–9

11 Takatsu H, Scheffel U, Fujiwara H. Sympathetic tone assessed by washout of iodine 125-labeled metaiodobenzylguanidine from the murine left ventricle-influence of immobilization stress and inhibition of the renin-angiotensin system. *J Nucl Cardiol* 1995; **2**: 507–12

12 Gascon P, Ley TJ, Toltzis RJ, Bonow RO. Spontaneous subarachnoid hemorrhage simulating acute transmural myocardial infarction. *Am Heart J* 1983: **105**; 511–3

13 Bates ER, Krell MJ, Dean EN, O'Neill WW, Vogel RA. Demonstration of the 'no-reflow' phenomenon by digital coronary arteriography. *Am J Cardiol* 1986: **57**; 177–8

14 Schoffer J, Montz R, Mathey D. Scintigraphic evidence of the 'no-reflow' phenomenon in human beings after coronary thrombolysis. *J Am Coll Cardiol* 1985: **5**; 593–8

15 Chesebro JH, Knatterud G, Roberts R *et al.* Thrombolysis in Myocardial Infarction (TIMI) trial phase I: a comparison between intravenous plasminogen activator and intravenous streptokinase. clinical findings through hospital discharge. *Circulation* 1987; **76**: 142–54

16 Piana RN, Paik GY, Moscucci M *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; **89**: 2514–18

17 Rŏth E. Effect of Ca-antagonists, beta-blockers and antioxidant during reperfusion period. *Bratisl Lek Listy* 1991; **92**· 195–200

18 Rŏth E, Matos G, Guarnieri C *et al.* Influence of the beta-blocker therapy on neutrophil superoxide generation and platelet aggregation in experimental myocardial ischemia and reflow. *Acta Physiol Hung* 1995; **83**: 163–70

19 Komaru T, Lamping KG, Eastham CL, Dellsperger KC. Role of ATP-sensitive potassium channels in coronary microvascular autoregulatory responses. *Circ Res* 1991; **69**. 1146–51

20 Auchampach JA, Cavero I, Gross GJ. Nicorandil attenuated myocardial dysfunction associated with transient ischemia by opening ATP-dependent potassium channels. *J Cardiovasc Pharmacol* 1992; **20**: 765–71

British Journal of Anaesthesia 84 (4): 514–7 (2000)

Spinal cord infarction and tetraplegia—rare complications of meningococcal meningitis

R. O'Farrell[1]*, J. Thornton[2], P. Brennan[2], F. Brett[3] and A. J. Cunningham[1]

[1]Departments of Anaesthesia/Critical Care Medicine, [2]Radiology and [3]Pathology, Beaumont Hospital/Royal College of Surgeons in Ireland, Dublin 9, Ireland

**Corresponding author: Department of Anaesthesia and Critical Care Professorial Unit, Beaumont Hospital, Dublin 9, Ireland*

A previously healthy 25-yr-old female developed flaccid areflexic tetraplegia, with intact cranial nerve function, 36 h after the diagnosis of bacterial meningitis. Polymerase chain reaction studies of cerebrospinal fluid and blood were positive for *Neisseria meningitidis*, serogroup B. Magnetic resonance of the cervicothoracic spine revealed increased signal intensity and expansion in the lower medulla, upper cervical cord and cerebellar tonsils. Neurosurgical consultation recommended hyperventilation, dexamethasone and regular mannitol therapy rather than decompressive intervention. The clinical course over the following 12 days was complicated by the development of progressive central nervous and multisystem organ failure with disseminated intravascular coagulopathy. Autopsy revealed cerebral oedema with cystic infarction extending from the medulla to the upper cervical cord and cerebellar tonsils. Flaccid areflexic tetraplegia with spinal cord infarction has not been reported following bacterial infection in an adult. The clinical implications would suggest complete central nervous system evaluation of patients recovering from meningococcal meningitis, since spinal cord lesions, although uncommon, do occur. In those very rare situations where a patient develops significant peripheral neurological deficits, urgent magnetic resonance imaging is warranted, to rule out an infective focus or an underlying anatomical anomaly.

Br J Anaesth 2000; **84**: 514–7

Keywords: complications, meningitis, meningococcal; complications, tetraplegia; complications, spinal cord infarction

Accepted for publication: November 24, 1999

Potentially pathogenic meningococci are present in 2–10% of the asymptomatic, healthy population.[1] These organisms tend to colonize the nasopharynx as a result of the high carbon dioxide tension and humidity, and the presence of specific receptor substances synthesized in the nasopharynx, to which they adhere.[2] Invasiveness depends solely on the amount of host-specific anti-meningococcal bactericidal antibody. A history of recent upper respiratory tract infection is common.

Neisseria meningitidis is the most common pathogen associated with acute bacterial meningitis in young adult populations.[1] The prevalence of bacterial meningitis depends on seasonal and geographic factors. In Ireland in 1997 the incidence was reported to be 5.1 per 100 000 population, one of the highest in Western Europe.[3] Reported cases peak in the winter months between December and March. The most common serogroup, B, for which there is no commercially available vaccine, has a 9% mortality rate.[3]

There are very few clinical reports of spinal cord injuries associated with purulent meningitis, although there have been isolated reports of arachnoiditis with secondary vascular compromise to the spinal cord.[4] The arachnoiditis is a result of a vasculitis with or without capillary thrombosis, or focal haemorrhage within the cord.

Drowsiness, lateralizing neurological signs or cranial nerve palsies may be indicative of severe cerebral oedema or other complications, such as hydrocephalus or venous sinus thrombosis associated with bacterial meningitis. Flaccid areflexic tetraplegia with spinal cord infarction has not been previously reported as a complication following *N. meningitidis* infection in an adult.

Case report

A previously healthy 25-yr-old female presented to another hospital in a comatose state. Information obtained at the time of presentation indicated she had been drinking alcohol the previous evening, and the following day she had complained of malaise, headache and vomiting, which was attributed to the consequences of alcohol intoxication.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Twelve hours later she was unresponsive, and the Glasgow coma score was 3 on presentation. Physical examination revealed a peripheral temperature of 38°C, heart rate 106 beats min^{-1} and arterial pressure 150/80 mm Hg. The pupils were dilated, unequal and unreactive to direct and consensual light. Deep tendon reflexes were absent in the left upper and lower extremities as were plantar responses bilaterally. Laboratory investigations included haemoglobin 12.1 mmol litre^{-1}, white cell count 35×10^9 litre^{-1}, serum urea 2.5 mmol litre^{-1}, serum creatinine 59 μmol litre^{-1} and serum glucose 7.6 mmol litre^{-1}. Initial management included the administration of benzylpenicillin 2.4G and cefotaxime 3G intravenously and tracheal intubation with intermittent positive pressure ventilation.

The patient was transferred to this hospital for urgent computer tomographic (CT) brain scan. The differential diagnosis included acute meningitis and subarachnoid haemorrhage. Non-contrast CT of brain revealed no intracerebral space-occupying lesion and there was no evidence of raised intracranial pressure. The pupils were of equal size and were reactive to light. The cerebrospinal fluid (CSF) was turbid at lumbar puncture. Subsequent microscopy confirmed severe, predominantly polymorphic, pleocytosis. Gram stain revealed the presence of Gram-negative diplococci. No organism was cultured, possibly because high-dose antibiotics had been given 2 h previously. Polymerase chain reaction studies of CSF and blood were positive for *N. meningitidis*, serogroup B.

Patient management included sedation, hypocapnic (Pa_{CO_2} 4.0–4.5 kPa) artificially controlled ventilation and cefotaxime 2G intravenously every 4 h. The clinical course over the following 12 h was complicated by pupillary dilation and haemodynamic instability attributed to brain stem compression or cerebral oedema and was treated with mannitol and inotropic agents. Repeat non-contrast CT examination demonstrated patent basal cisterns.

Twenty-four hours later, following withdrawal of sedation, the patient was alert and obeyed commands by moving her eyes and tongue. However, neurological assessment at 36 h revealed flaccid areflexic tetraplegia consistent with a lesion at the level of C1, with intact cranial nerve function. A magnetic resonance (MR) scan was performed urgently to rule out a subdural or epidural pyogenic collection. Sagittal views of the cervicothoracic spine revealed increased signal intensity and expansion in the lower medulla, upper cervical cord and cerebellar tonsils. There was tonsillar ectopia with enhancement of the surrounding meninges. The CSF at the foramen magnum was effaced, indicating compression. The fourth ventricle was patent. Neurosurgical consultation recommended dexamethasone and regular mannitol therapy rather than decompressive surgical intervention.

The subsequent clinical course was complicated by the development of pyrexia (temperature 40°C) and leucocytosis (white cell count 28×10^9 litre^{-1}) 6 days later. No organisms were isolated on cultures. Repeat MR imaging showed persistent abnormality within the structures of the foramen magnum, with effacement of CSF. During the following 24 h, the patient became progressively obtunded and unresponsive with the onset of seizure activity. Inotropic support was initiated to treat haemodynamic instability. Antibiotic treatment was extended to cover possible central nervous system (CNS) *Listeria monocytogenes* or fungal infection. Over the final 6 days of her illness, she developed progressive CNS and multisystem organ failure and disseminated intravascular coagulation.

Autopsy revealed cystic infarction extending from the medulla to the upper cervical cord. An area of infarction, of similar age, was noted bilaterally in the cerebellar tonsils. The brain was very oedematous. There was no evidence of active CNS infection or residual meningitis. Fibrin deposition at the base of the brain indicated recent meningitis. The cerebellum had widespread hypoxic changes, but the pons was normal. The lungs showed evidence of acute respiratory distress syndrome, and the kidneys showed changes associated with acute tubular necrosis. Autolytic changes were reported in the adrenal glands and liver.

Discussion

Nasal mucosal colonization with *N meningitidis* may be followed by consequences ranging from transient bacteraemia with no sequelae, to the rare entities of chronic meningococcaemia, clinical meningitis or fulminant meningococcaemia. The incidence of coexisting meningitis and meningococcaemia can range from 12% to 61%.[1] Interestingly, the presence of meningitis has been shown to reduce the risk of meningococcaemia proving fatal.[5] Improved survival rates in recent years have been attributed to increased awareness of the disease, combined with aggressive supportive therapy with volume replacement, artificial ventilation, inotropic support and renal replacement therapy.[6] Third-generation cephalosporins are the recommended first-line agents in acute bacterial meningitis until sensitivity reports are available because of reported resistant strains of *Streptococcus pneumoniae* in the United Kingdom and mainland Europe.[7]

The development of flaccid areflexic tetraplegia with intact cranial nerve function, 36 h after *N. meningitidis* infection, suggested the possibility of a subdural or epidural empyema or transverse myelitis at the craniocervical level. MR imaging excluded extrinsic cord compression while the increased signal intensity and expansion in the lower medulla, upper cervical cord and cerebellar tonsils on sagittal views of the cervicothoracic spine suggested transverse myelitis. There was also MR evidence of tonsillar ectopia with enhancement of the surrounding meninges.

Transverse myelitis is an extremely rare, monophasic, inflammatory demyelinating illness, with a reported annual incidence of 1.3–4 per million population.[8] Characteristically, acute inflammation of the spinal cord results in flaccid paraparesis or tetraparesis, with a defined sensory level. To date, the only case report of transverse myelitis complicating bacterial meningitis was in a preterm neonate with streptococcus group B infection.[9] Transverse myelitis is normally associated with viral infections such as herpes, varicella, Epstein–Barr virus or hepatitis A. It has also been reported in systemic bacterial or atypical infections such as syphilis, mycoplasma or Lyme disease.[10] [11] Although mostly inflammatory in origin, predisposing conditions include multiple sclerosis and anterior spinal artery occlusion. The differential diagnosis of acute flaccid paralysis would also include Guillain–Barré syndrome, poliomyelitis, central pontine myelinolysis and acute cerebellitis.

Autopsy findings suggested that the cause of tetraplegia in this case was infarction of the craniocervical spinal cord. Histopathological findings dated the spinal cord infarction to approximately 12 h after admission when clinical signs of brainstem compression were noted. MR imaging about this time showed increased signal intensity within the medulla and upper cord and effacement of CSF at the foramen magnum, indicating significant compression of these structures. Of note, there was no mass effect in the supratentorial compartment and fossa, with persistent patency of the fourth ventricle.

The presence of pre-existing tonsillar ectopia may have predisposed this patient to subsequent spinal cord infarction. This anatomical anomaly is well described. In normal asymptomatic patients, the mean position of the cerebellar tonsils ranges from 8 mm above the foramen magnum to 5 mm below it.[12] Up to 14% of the adult population have tonsils extending slightly below the foramen magnum; 5 mm below it is taken as the normal cut-off point. This degree of ectopia is, under normal circumstances, of no clinical significance. If the tonsils are lower than 3 mm, this constitutes a Chiari I malformation[12]—an anomaly with inconsistent clinical findings, which tends to manifest itself in early to middle adult life.

Acute bacterial meningitis superimposed on such anatomy may exacerbate the degree of tonsillar ectopia, because of local tonsillar oedema and the mass effect from the inflammatory process occurring at the foramen magnum level, thus compromising the enclosed structures. The consequent vascular compromise, with ischaemia and infarction of the upper cervical cord and cerebellar tonsils, might be manifest clinically by flaccid areflexic tetraplegia. CT imaging of the base of the skull may have limited application in such patients, because the structures of the foramen magnum may not be adequately seen. MR imaging is recommended as the investigation of choice in any patient with evidence of craniocervical pathology.[13]

Glucocorticoids are now extensively used, especially in the paediatric population, in the treatment of meningitis. There is evidence that they reduce the indices of meningeal inflammation in the CSF, and attenuate the rise in levels of tumour necrosis factor if given before the administration of ceftriaxone to patients with *Haemophilus influenzae* and *S. pneumoniae* meningitis.[14] Two studies have suggested that steroid-treated patients have improved neurological and audiological outcomes in meningococcal meningitis.[15] Most studies advocate administering dexamethasone at, or before, the first dose of antibiotic, in order to attenuate the rise in cytokines associated with antibiotic-induced bacteriolysis.

Decompressive surgery was considered as a treatment option in this patient, but was not subsequently performed. To perform foramen magnum decompression on such an unstable patient requires supportive risk–benefit data to be available. However, case reports have described beneficial patient outcomes following emergency decompressive surgery of the craniocervical region, particularly in cases of spontaneous epidural haematoma. Critical factors for neurological recovery include the vertebral level of cord pathology, extent of pre-operative sensorimotor deficit and time interval between presentation and surgery. Thirty-six hours has been claimed to be the critical operative interval.[16] Emergency surgery should be performed, irrespective of the neurological dysfunction, in cases of spinal epidural abscess.[17]

Furuya and colleagues published clinical trial data on patients with symptomatic cerebellar tonsillar ectopia and compared them to patients with asymptomatic ectopia and to matched controls.[18] The subjects were evaluated with MR studies and precise neurotological examination. Depending on clinical and MR findings, posterior fossa decompression surgery was performed. After the operation, all patients displayed improvement in symptoms and less severe neurotological abnormalities. The authors concluded that tonsillar ectopia, *per se*, could cause neurological symptoms which were surgically treatable.

References

1 Kennedy NJ, Duncan AW. Acute meningococcaemia: recent advances in management (review). *Anaesth Intens Care* 1996; **24**: 197–216

2 Ison C, Neisseria, infection and immunity. In: Roitt IM, Delves PJ, eds. *Encyclopedia of Immunology*. London; Academic Press, 1992; 1139–40

3 Fogarty I, Cafferky MT, Maloney AC. Meningococcal disease in the Republic of Ireland. *Commun Dis Rep CDR Rev* 1997; **7**: R9–13

4 Glista GG, Sullivan T, Brumlik J. Spinal cord involvement in acute bacterial meningitis. *J Am Med Assoc* 1980; **243**: 1362–3

5 Algren JT, Suresh L, Cutliff SA. Predictions of outcome in acute meningococcal infection in children. *Crit Care Med* 1993; **21**: 447–52

6 Smith OP, White B, Vaughan D *et al.* Use of protein-C concentrate, heparin, and haemodiafiltration in meningococcus-induced purpura fulminans. *Lancet* 1997; **350**: 1590–3

7 Goldstein FW, Garau J. Thirty years of penicillin-resistant *S. pneumoniae*: myth or reality? *Lancet* 1997; **350**: 233–4

8 Shian WJ, Chi CS. Acute transverse myelitis. *Chung Hua I Hsueh Tsa Chih Taipei* 1994; **54**: 57–61

9 Puvabanditsin S, Wojdylo EW, Garrow E, Kalavantavanich K. Group B strep. meningitis: a case of transverse myelitis with spinal cord and posterior fossa cysts. *Pediatr Radiol* 1997; **27**: 317–8

10 Abele-Horn M, Franck W, Busch U. Transverse myelitis associated with *Mycoplasma pneumoniae* infection. *Clin Infect Dis* 1998; **26**: 909–12

11 Olivares JP, Pallas F, Ceccaldi M, Viton JM, Raoult D, Delarque A. Lyme disease presenting as isolated acute urinary retention caused by transverse myelitis: an electrophysiological and urodynamical study. *Arch Phys Med Rehab* 1995; **76**: 1171–2

12 Barkovich AJ, Wippold FJ, Sherman JL, Citrin CM. Significance of cerebellar tonsillar position on MR. *AJNR* 1986; **7**: 795–9

13 Ishikawa N, Kikuchi H, Fujisawa I, Yonekawa Y. Tonsillar herniation on magnetic resonance imaging. *Neurosurgery* 1988; **22**: 77–81

14 Mustafa MM, Ramilo O, Mertsola J *et al.* Modulation of inflammation and cachetin activity in relation to treatment of experimental *Haemophilus influenzae* type B meningitis. *J Infect Dis* 1989; **160**: 818–25

15 Syrogiannopoulos GA, Lourida AN, Theodoridou MC Dexamethasone therapy for bacterial meningitis: 2 versus 4 day regimen. *J Infect Dis* 1994; **169**. 853–8

16 Groen RJ, Van Alphen HA. Operative treatment of spontaneous spinal epidural haematomas: a study of the factors determining post-operative outcome (review). *Neurosurgery* 1996; **39**. 494–508

17 Del Curling O, Gower DJ, McWhorter JM. Changing concepts in spinal epidural abscess: a report of 29 cases. *Neurosurgery* 1990; **27**: 185–92

18 Furuya K, Sano K, Segawa H, Ide K, Yoneyama H. Symptomatic tonsillar ectopia. *J Neurol Neurosurg Psychiatry* 1998; **64**· 221–6

British Journal of Anaesthesia 84 (4): 518–20 (2000)

Cranial subdural haematoma associated with dural puncture in labour

D. J. A. Vaughan*, C. A. Stirrup and P. N. Robinson

Department of Anaesthesia, Northwick Park and St Mark's Hospitals, Watford Road, Harrow, Middlesex HA1 3UJ, UK

**Corresponding author*

A 23-yr-old primagravida sustained a dural puncture during epidural catheter insertion and developed a headache that settled with oral diclofenac and codydramol. On the third day after delivery, she convulsed twice without warning. As plasma urate was increased, the putative diagnosis of an eclamptic fit was made, and magnesium therapy was started. A contrast CT scan revealed that the cause of the patient's symptoms was a subdural haematoma with raised intracranial pressure. A coincidental arteriovenous malformation was noted. This case emphasises the need to consider the differential diagnoses of post-partum headache. The management of acute intracranial haematoma is described.

Br J Anaesth 2000; **84**: 518–20

Keywords: analgesic techniques, epidural; complications, headache; complications, seizure; complications, subdural haematoma

Accepted for publication: December 6, 1999

Inadvertent dural puncture with subsequent headache is a recognized complication of epidural analgesia.[1] This case report emphasizes the need for careful and ongoing assessment of these patients in order to ensure that less common causes of headache are not overlooked.

Case report

A 23-yr-old primiparous Indian woman presented in labour following spontaneous rupture of membranes at home. She was distressed and requesting epidural analgesia. The combination of a high body mass index (height 144 cm, weight at last antenatal clinic before delivery 82 kg; body mass index 39.5) and a poorly compliant and distressed patient made epidural catheter insertion difficult, and in the process an inadvertent dural puncture occurred. The catheter was sited at a higher level, and good analgesia was obtained with a test dose of 0.25% bupivacaine 3 ml, followed by a further 10 ml with fentanyl 50 μg. Subsequent top-ups by the anaesthetist with 0.1% bupivacaine 10 ml plus fentanyl 2 μg ml^{-1} provided good analgesia without side-effects.

The contractions were augmented with an oxytocin infusion, as meconium was present in the liquor. Four hours after the epidural, the patient developed low-grade pyrexia (37.8°C) and was started on amoxycillin and clavulanic acid (co-amoxiclav 1.2 g) i.v.; a blood culture was taken. After a further 3 h the patient was fully dilated and started to push. At this time she began to complain of a continuous, dull, moderate occipital headache with no radiation. In view of the pyrexia, meconium and a worsening cardiotocograph trace, a forceps delivery was performed.

Overnight, the patient complained of severe occipital headache, although this settled with paracetamol and rest. This was assumed to be a post-dural puncture headache (PDPH) because it had a postural component (it was worse on sitting up or standing). Over the next 2 days the patient was regularly reviewed and her headache improved rapidly with oral codydramol and diclofenac. At no time did she complain of nausea, vomiting, photophobia or neck stiffness. Her pyrexia settled within a day of delivery. On the third postnatal day, it was agreed that a blood patch was not indicated and discharge was planned for the next day.

That evening, the patient had two self-limiting 30 s tonic–clonic convulsions. After 30 min of post-ictal drowsiness, the patient was fully alert with a Glasgow coma score of 15. The only abnormal findings on examination were symmetrical, moderately brisk reflexes. A putative diagnosis of eclamptic fits was made, strengthened by a raised plasma urate level of 438 μmol $litre^{-1}$ (normal range 100–400 μmol $litre^{-1}$). Blood pressure was normal, and there was no significant proteinurea or oedema. A raised white cell count of 17.5×10^9 ml^{-1}, consisting mainly of neutrophils, was noted. High dependency care was initiated and magnesium therapy started as per unit protocol (magnesium sulphate 4 g i.v. as a slow bolus followed by an infusion of 1 g hourly).

After a stable night during which the occipital headache recurred, the obstetric anaesthetic consultant reviewed the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

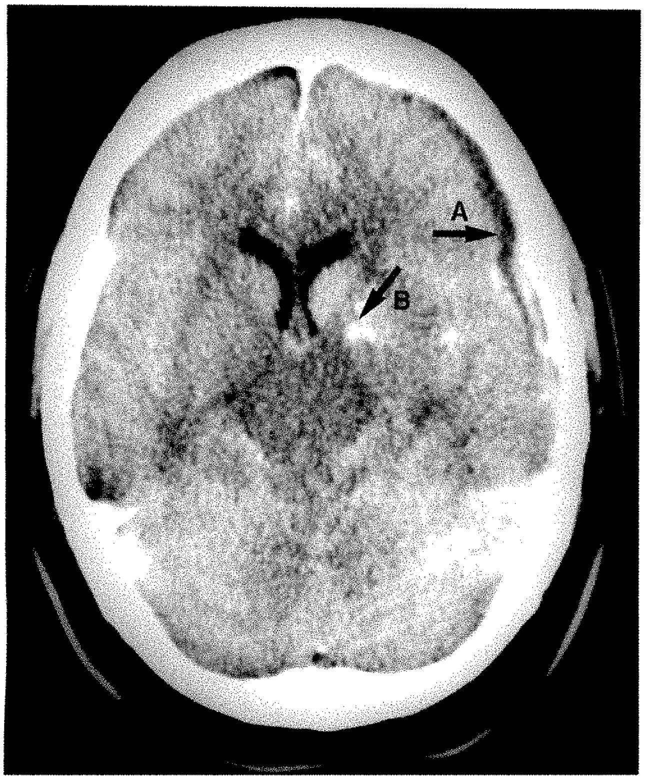


Fig 1 Contrast-enhanced cerebral CT scan showing (A) small subdural haematoma with an outer, posterior layer of fresh blood and (B) AVM arising from the basal ganglia.

patient. It was felt that the onset of PDPH during labour, combined with a tonic–clonic seizure 3 days after delivery, warranted an urgent computerized tomography (CT) scan to exclude intracranial pathology. Contrast-enhanced CT revealed a left-sided subdural haematoma, evidence of raised intracranial pressure without midline shift, and an arteriovenous malformation (AVM) in the basal ganglia (see Fig. 1).

The patient was transferred to a neurosurgical centre where she returned to a symptom-free state without intervention. A cerebral magnetic resonance imaging (MRI) scan revealed no further information. It has been decided to manage her conservatively with regular neurological follow-up.

Discussion

This case illustrates the difficulties of diagnosing the cause of headache and convulsions in the peripartum period. The differential diagnosis of post-delivery headache in this case includes PDPH, pre-eclamptic headache, subdural or subarachnoid haemorrhage, simple tension or migraine headache, meningitis and cortical vein thrombosis.[1] With the knowledge that dural puncture had occurred earlier in labour and from the postural component of this headache, it was assumed that PDPH was the most likely diagnosis. However, the onset of the headache was early, coinciding with the second stage of labour and the initiation of pushing, making the diagnosis of PDPH less likely. The diagnosis of pre-eclampsia as the causal condition was discounted, as no other symptoms were present. Subdural or subarachnoid haemorrhage were not considered at the time of onset of the headache, as these are extremely rare causes to present *de novo*. It was only when the convulsions occurred that this omission from the differential diagnosis was corrected. Other than an initial neutrophilia, there were no features to support a diagnosis of meningitis at this time; the pyrexia settled and the white count normalized. The history was not suggestive of cortical vein thrombosis, and this was excluded later on MRI scanning.

The differential diagnosis of the convulsions in this case includes eclampsia, intracranial haemorrhage, embolic episodes and epilepsy. Local anaesthetic toxicity can be excluded as the convulsion occurred on the third day after delivery. Subdural haematoma following dural puncture is a very rare complication of epidural analgesia in labour, and may be cranial or spinal.[2–5] The cause is low cerebrospinal fluid pressure following dural puncture leading to traction and tearing of thin-walled dural blood vessels.[6] In this case the onset of the headache was very early in relation to the time of dural puncture. It is unusual for a large CSF leak to have occurred in this short time. We have assumed that the tear and subsequent bleeding occurred at or around the time of onset of headache in labour. However, this may have been a tension or stress-related headache, and the pathological events may have occurred later that evening. It is not possible to pinpoint the time of vessel rupture definitively.

Cranial subdural haematomas may present acutely, subacutely or chronically with a variety of complaints including headache, altered level of consciousness or even psychiatric symptoms.[7] Acute subdural haematomas have been described as lesions causing signs or symptoms within 7 days of the bleed. Spinal subdural haematomas following epidural anaesthesia are extremely rare and of complex presentation.[6] [8] The presence of a suspected PDPH complicated by neurological deterioration, as in this case, should prompt a search for intracranial pathology.

The plain CT scan did not reveal the underlying pathology, and the subdural haematoma and AVM were only seen after contrast enhancement. CT may not show subdural haematomas without contrast, and this has previously been reported as a cause of delayed diagnosis.[9] Haemorrhage from the AVM at the time of pushing is a possible cause of the subdural haematoma but, more commonly, ruptured AVMs cause subarachnoid bleeding.

It was considered by the neurosurgeon and neuroradiologist that the AVM seen on CT was an incidental finding and that the subdural haematoma was secondary to the dural puncture. The raised intracranial pressure was a result of the haematoma and its increasing space-occupying effect because of oedema. This is in marked contrast to the low CSF pressure believed to have caused the vessel tear.

Haemorrhage from an AVM is most common in women under 25 yr and is most likely during the second trimester and in the immediate post-partum period.[10] The clinical presentation is sudden onset of headache, often accompanied by nausea and vomiting, photophobia, seizure activity, and focal motor and sensory disturbances.[11] In this case, the onset of headache coincided with initiation of pushing, arousing suspicion—in retrospect—of an intracranial event. Subarachnoid haemorrhage only occurs in one in 10 000 pregnancies, but is associated with a high maternal mortality.[12]

The management of subdural haematoma is either conservative (clinical observation and possible intracranial pressure monitoring) or surgical evacuation. For this reason the patient was transferred to a neurosurgical unit. In view of the small size of the haematoma coupled with a rapid return to normal neurological status, conservative management was deemed appropriate. Haematomas under 5 mm often spontaneously resolve. In cases requiring surgery, preoperative neurological status affects postoperative survival. Early haematoma evacuation and young age are favourable prognostic factors. This patient had no midline shift on CT scan although there was evidence of raised intracranial pressure. Parenchymal injury causes midline shift and is associated with decreased survival.[13]

This case also raises the issue of when a blood patch for PDPH should be performed. Reynolds recommends that, 'Headache after dural puncture with a large needle should be treated promptly with an epidural blood patch'.[14] Our unit policy is to assess all known dural punctures for blood patching after 24 h bed rest, hydration and analgesia. In this case, the patient improved rapidly with conservative measures and it was felt that a patch was not necessary. It could be argued that early blood patching may decrease the risk of subdural bleeding by preventing a fall in CSF pressure. In this patient such action probably would not have helped, as we believe the bleeding occurred during labour. It is our practice to discharge patients with PDPH 24 h after a successful blood patch, or when they are mobile in conservatively managed cases. All patients are reviewed in the obstetric anaesthetic clinic 1–2 weeks later to ensure that symptoms have not recurred or worsened, and are advised to contact the obstetric anaesthetist if any symptoms occur or recur. We feel that this follow-up minimizes the risk of late complications being missed.

The management of PDPH is often complex and is an important role for the obstetric anaesthetist. While we emphasize the rarity of subdural haematoma as a complication of dural puncture, this case highlights the importance of including it in the differential diagnosis. We suggest the urgent use of contrast-enhanced CT in all cases of seizure after dural puncture to exclude intracranial bleeding.

References

1 Berger CW, Crosby ET, Grodecki W. North American survey of the management of dural puncture occurring during labour epidural analgesia. *Can J Anaesth* 1998; **45**: 110–4

2 Diemunsch P, Balabaud VP, Petiau C, Marescaux C, Muller A. Bilateral subdural haematoma following epidural anaesthesia. *Can J Anaesth* 1998; **45**: 328–31

3 Skoldefors EK, Olofsson CI. Intracranial subdural haematoma complicates accidental dural tap during labour. *Eur J Obstet Gynecol Reprod Biol* 1998; **81**: 119–21

4 Pavlin DJ, McDonald JS, Child B, Rusch B. Acute subdural haematoma—an unusual sequel to lumbar puncture. *Anesthesiology* 1979; **51**: 338–40

5 Jack TM. Post partum intracranial haematoma. A possible complication of epidural analgesia. *Anaesthesia* 1979; **34**: 176–80

6 Russell IF. Post partum neurological problems. In: Russell IF, Lyons G, eds. *Clinical Problems in Obstetric Anaesthesia*. London: Chapman and Hall Medical, 1997; 149–60

7 Campbell DA, Varma TRK. Chronic subdural haematoma after lumbar subarachnoid analgesia for caesarean section, presenting as puerperal psychosis. *Br J Obstet Gynaecol* 1993; **100**: 782–4

8 Roscoe MWA, Barrington TW. Acute spinal subdural haematoma: a case report and review of the literature. *Spine* 1984; **9**: 672–5

9 Wyble SW, Bayhi D, Webre D, Viswanathan S. Bilateral subdural haematomas after dural puncture: delayed diagnosis after false negative CT scan without contrast. *Reg Anesth* 1992; **17**: 52–3

10 Bromage PR. Neurologic complications of regional anesthesia in obstetrics. In: van Zundert A, Ostheimer GW, eds. *Pain Relief and Anesthesia in Obstetrics*. New York: Churchill Livingstone 1996; 993–1004

11 Robinson JL, Hall CS. Arteriovenous malformations and aneurysms. *J Neurosurg* 1974; **41**: 63–70

12 Yih PS, Cheong KF. Anaesthesia for caesarean section in a patient with an intracranial arteriovenous malformation. *Anaesth Intensive Care* 1999; **27**: 66–8

13 Ogilvy CS, Barker FG. Head injury. In: Bogousslavsky J, Fisher M, eds. *Textbook of Neurology*. Boston: Butterworth–Heinemann 1998; 711–25

14 Reynolds F. Dural puncture and headache. *Br Med J* 1993; **306**: 874–6

British Journal of Anaesthesia **84** (**4**): 521–4 (2000)

Delayed bilateral internal carotid artery thrombosis following accidental strangulation

S. H. Kiani[1] [2]* and D. C. Simes[1]

[1]*Department of Intensive Care Medicine, Fremantle Hospital, Alma Street, Fremantle, Western Australia, Australia.* [2]*Department of Anaesthesia, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK*

**Corresponding author*

A 24-yr-old male presented after a fishing accident in which he was pulled underwater by a rope attached to a crayfish pot. He was winched out of the water with the rope still around his neck, sustaining serious neck injuries that ultimately led to his death. After initial resuscitation, he remained fully conscious for approximately 8 h, after which there was a rapid and sudden deterioration in his level of consciousness. The presentation, investigation, management and subsequent postmortem findings are presented and discussed.

Br J Anaesth 2000; **84**: 521–4

Keywords: arteries, internal carotid; complications, trauma

Accepted for publication: November 5, 1999

Bifurcation of the common carotid arteries in the neck leads to the formation of the internal and external carotid vessels. The two internal carotid arteries, along with the vertebral arteries, are responsible for the blood supply to the brain, uniting on its inferior surface to form the circulus arteriosus. During their short course in the neck, the internal carotid arteries are thus vulnerable to both penetrating and blunt trauma.

This report illustrates an unusual form of blunt trauma to the neck leading to the rare occurrence of bilateral internal carotid artery occlusion and delayed onset of neurological signs.

Case report

A previously fit 24-yr-old male was transferred to our emergency department by an air ambulance from a peripheral hospital. Eight hours earlier, he had been involved in an accident on a fishing boat in which he was dragged overboard and underwater by a rope around his neck attached to a heavy crayfish pot (weighing approximately 100 kg). He was submerged for more than 60 s at a depth of around 40 feet. His colleagues hoisted him out of the sea and onto the deck using the same rope. On surfacing he was found to be apnoeic, cyanosed and unresponsive. He was given expired air resuscitation for about 10 min by the crew, which led to resumption of spontaneous respiration. A peripheral pulse was present throughout the resuscitation.

On assessment at the peripheral hospital (3 h later), he was fully conscious and orientated, with a core temperature of 35°C. He had vomited once during the journey. Examination revealed bilateral conjunctival haemorrhages; reactive pupils with 1-mm inequality; engorged and tender ears; a swollen neck with a horizontal abrasion marking the position of the rope (at the level of the thyroid cartilage); and mild left arm weakness. Initial haematological investigations were unremarkable, and chest and cervical spine radiographs revealed no abnormalities.

In view of the limited medical resources at the peripheral hospital, he was transferred by air ambulance to a larger facility. Throughout the journey he remained fully conscious and haemodynamically stable. He arrived approximately 8 h after the accident.

In the emergency department, he was noted to have an initial Glasgow Coma Score of 15 but within 20 min he lost consciousness. The trachea was rapidly intubated. At laryngoscopy, the larynx was found to be deviated to the left and the oesophageal opening to the right. Nevertheless, the trachea was intubated with ease.

In view of the sudden deterioration, associated neck injury and history of submersion, urgent CT imaging of the head and neck and carotid angiography were performed. At this stage, the patient remained haemodynamically stable, and was sedated, paralysed and artificially ventilated to normocarbia.

CT imaging revealed gross cerebral oedema and soft tissue oedema of the neck. Carotid angiography revealed bilateral occlusion of the internal carotid arteries (Fig. 1A and B). Urgent bilateral carotid revascularization was therefore performed using saphenous vein grafts. Carotid arterial shunts were used to bypass the occlusion. Monitoring

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

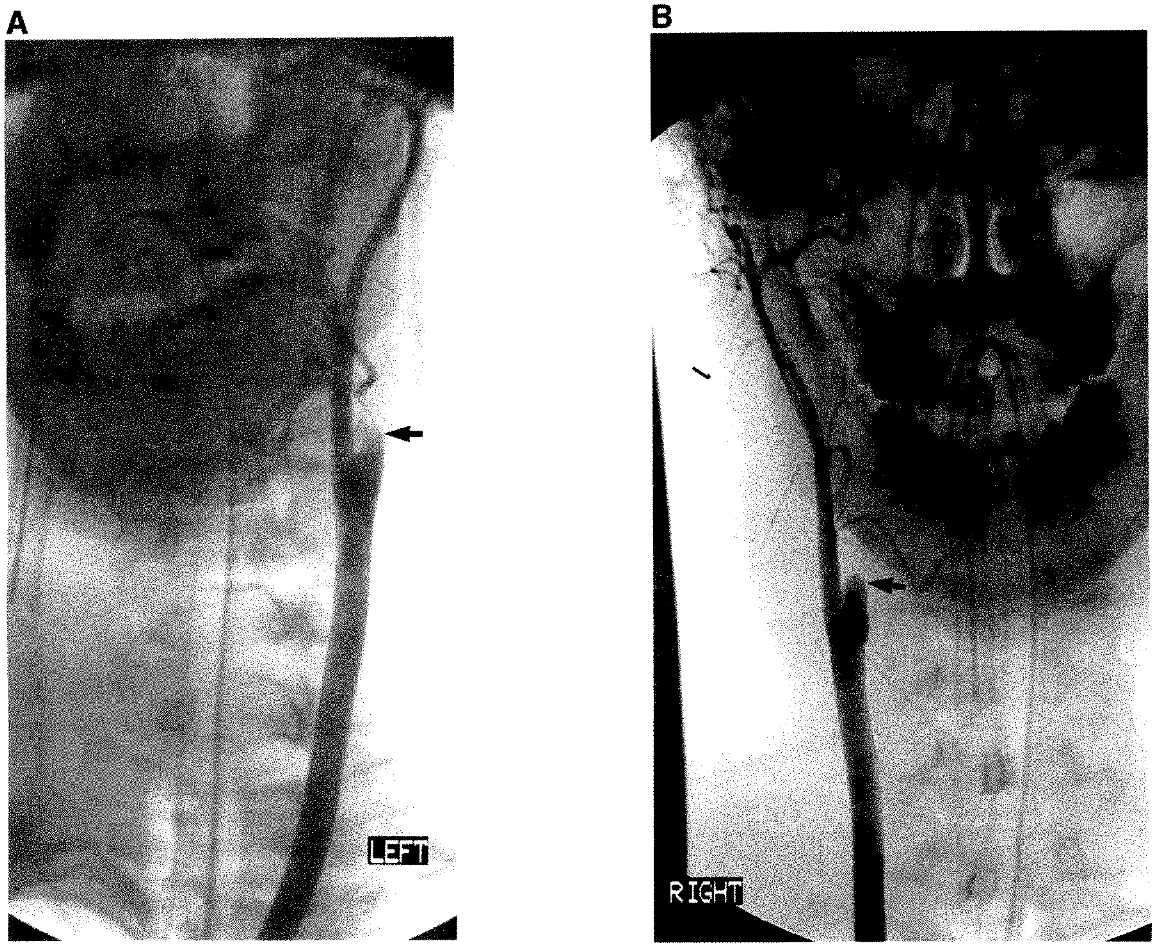


Fig 1 Carotid angiograms illustrating (A) left and (B) right internal carotid artery thrombosis.

of the cerebral circulation during the operation (e.g. by transcranial Doppler) was not available. The patient was admitted to the intensive care unit after the operation. Check angiography during the operation revealed satisfactory blood flow in the right internal carotid and good flow on the left. There were no problems during the operation apart from hypertension (mean arterial pressure more than 110 mm Hg), which was not treated by the anaesthetist in order to maintain cerebral blood flow. Mannitol and artificial ventilation to normocarbia were used in view of the known cerebral oedema.

In the intensive care unit, a parenchymal intracranial pressure monitor was sited. Initial intracranial pressure was grossly elevated (up to 70 mm Hg) and refractory to maximal osmotherapy, intermittent hyperventilation for exacerbations of intracranial hypertension, and sedation and analgesia with large doses of midazolam and morphine. Cerebral perfusion pressure was maintained at >75 mm Hg with inotropic support using norepinephrine and epinephrine. Focal neurological signs were also present, with an unreactive left pupil. A thiopental loading dose followed by infusion was started to treat the uncontrollable intracranial pressure. This remained high, however, peaking at 80 mm Hg over the next 12 h and requiring numerous bolus doses of thiopental, regular mannitol and hypertonic saline in order to keep it below 40 mm Hg.

Over the course of the next 72 h there was no improvement. The pupils became bilaterally fixed and dilated and brainstem reflexes were absent on clinical examination. Technetium scintigraphy and contrast angiography of the cerebral circulation were performed on two occasions 24 h apart in an attempt to ascertain whether perfusion to the brain was present, as the clinical diagnosis of brain death was made impossible by the thiopental infusion. Both investigations revealed some posterior circulation perfusion, but no supratentorial flow, suggesting re-thrombosis. In view of these findings, continuing support was futile and, after discussion with the family, treatment was withdrawn.

A post-mortem investigation concluded that the cause of death was consistent with cerebral ischaemia following vascular neck injury secondary to neck compression.

Discussion

This case presented an unusual combination of potential problems resulting from accidental near-drowning and near-hanging. The near-drowning aspect of the presentation did not appear to contribute significantly to the outcome, as no water was aspirated from the lungs and at no time was lung function impaired. Although expired air resuscitation was performed initially, the only other finding that could be attributed to the submersion was mild hypothermia. One may argue that the elevated intracranial pressure and cerebral oedema could have been attributable to cerebral hypoxaemia resulting from the initial submersion,[1] but the patient was fully conscious and orientated for a significant length of time after the incident and the submersion time was short.

Another mechanism of injury may explain the subsequent course. The presence of the rope around the neck and the subsequent survival allow us to refer to the injury as a near-hanging.[2] The mechanism of the injury is different from most near-hangings, as there would have been no initial sudden axial traction from suspension[3] because of the presence of the surrounding water to support the weight of the body.

In this case, the injuries were more likely sustained after attempts at removal from the water by his colleagues. As they winched him back up to the surface, there would have been a period between exiting the water and reaching the deck when he would have been suspended by his neck, the forces of the winch and the pursuing craypot acting in opposite directions and tightening the rope. This would lead to continual external pressure on his neck, and thus a form of strangulation.

The contents of the anterior neck region are uniquely vulnerable to external pressure because of the number of vital structures in a relatively confined and unprotected space. Posteriorly, the spinal cord is at its most vulnerable, the cervical spine being more mobile but less stable than the thoracic and lumbar regions of the vertebral column.[3]

Structures at risk in hanging include the vasculature of the neck, the carotid bodies, the larynx and its associated cartilages, and the cervical spine. Secondary injury to the brain is the main cause of early death. Pulmonary complications are responsible for delayed mortality, often as a result of the acute respiratory distress syndrome, the exact pathogenesis of which is unclear in this setting,[4] although a centroneurogenic mechanism has been proposed.

No bony or cartilaginous damage was sustained in our patient. Cervical spine injuries are rare in non-judicial hanging[5] and depend on a significant drop length, of at least the height of the patient[6] (which was not relevant in this case).

The obvious clinical finding was gross swelling of the neck, which initially raised concerns of airway obstruction, although this was resolved on intubation. Venous obstruction and subsequent stagnant cerebral hypoxia has been proposed as the initial event in most hangings, but arterial obstruction is likely to play a more important role, particularly as loss of consciousness has been reported to occur as early as 15 s after suspension.[3] The force required to obstruct the carotids is only slightly greater than that for the jugular veins: 3.5 kg compared with 2 kg;[7] both of these values would easily be exceeded with only partial suspension of body weight.

Suspicion of vascular damage as a cause of the gross swelling of the neck led to visualization of the arterial vessels using angiography. This demonstrated bilateral internal carotid artery occlusion (Fig. 1A and B). Traction on arterial structures can lead to intimal damage and subsequent thrombosis and obstruction.[8] This was the most likely cause in this case, although it is a rare finding: an autopsy series of 101 hangings failed to demonstrate any intimal tears.[9]

Traumatic thrombosis of the internal carotid artery is reported as being caused by one of four mechanisms: injury to the intrapetrous or cavernous part of the carotid artery during basal skull fracture; injury to the point of emergence of the carotid artery from the cavernous sinus as the result of shearing strains; a direct blow to the neck or trauma to the paratonsillar area by a foreign object carried in the mouth; and stretching of the carotid artery by hyperextension and lateral flexion of the neck (which probably occurred in this case). Secondary symptoms resulting from thrombosis of the carotid artery develop most commonly between 12 and 24 h after the injury. The prognosis in these patients is mostly poor.[10]

By reviewing the history, the natural progression of the pathology can be elaborated upon. After initial resuscitation, the patient remained conscious for about 8 h. During this time, intimal damage of the carotid must have been present and the thrombotic process would have been developing. The time interval before onset of unconsciousness is typical of cases of blunt carotid trauma, as dissection of the intimal layer and progressive thrombosis can have a latency period of up to 24 h.[11] Deterioration after this period was likely to be due to the gross increase in intracranial pressure and the concomitant decrease in cerebral perfusion pressure, leading to loss of consciousness as a result of cerebral anoxia. Unfortunately, during the inevitable delay involved in obtaining the essential diagnostic imaging studies and corrective surgery, the intractable cerebral oedema meant that significant brain damage had already ensued before the patient was admitted to the intensive care unit, rendering futile subsequent attempts at controlling intracranial pressure.

It has been suggested that, after initial resuscitation, appropriate airway control and neurological examination, CT scanning of the head and neck and repeated colour-flow Doppler sonography are indicated in all patients with neck trauma of this nature.[11] If Doppler sonography reveals an intimal lesion, angiography and immediate surgery and reconstruction of the artery have been recommended, even if there is not yet a neurological deficit. Others recommend angiography in all patients with neurological symptoms.[12]

Thrombolysis has been used with success in cases of non-traumatic carotid thrombotic occlusion (stroke)[13] and has been suggested as an alternative to surgical correction in traumatic thrombosis. But there are no reports of bilateral

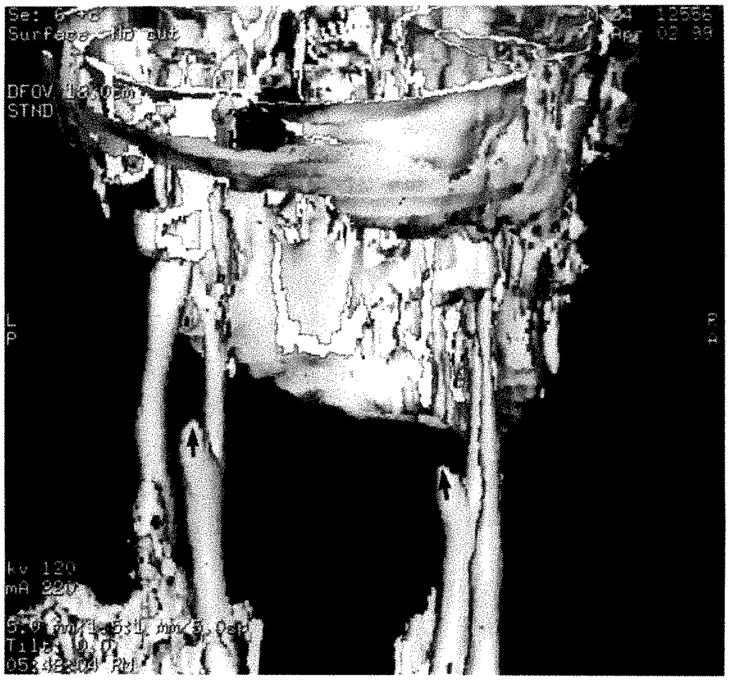


Fig 2 Computerized tomographic angiogram (posterior view). Arrows indicate the point of occlusion of the internal carotid vessels.

traumatic carotid thrombosis being treated with systemic or arterially directed thrombolysis. In our case, there was fear of the small retinal and cerebral haemorrhages enlarging with thrombolytic therapy, leading to blindness or significant intracranial bleeding and also interfering with definitive surgical repair.

There is an inevitable delay, as surgical intervention is dependent on accurate localization of the abnormality. Cerebral angiography is a time-consuming event in the presence of acute and profound ischaemic brain injury, delaying restitution of cerebral blood flow with inevitable neurological deterioration. Alternatively, computerized tomographic angiography uses the same technique as head and neck scanning and provides images that may be of adequate quality for emergency, life-saving surgery.

The computerized tomographic angiogram of this patient is presented in Figure 2. Our vascular surgeons consider records such as these to be sufficient to allow the patient to be taken directly to theatre without the delay of cerebral angiography. Timely intervention is vital for the best neurological result, and so where this technology is available it may provide a better outcome.

This case illustrates the need for a high index of suspicion of vascular injury in cases of blunt trauma to the neck, especially when the history suggests a significant degree of trauma from partial or full suspension. A period of normal consciousness and the absence of neurological signs is not uncommon in blunt injuries to the carotid vessels, and thus such cases present a diagnostic challenge.

References

1 Gonzalez-Rothi RJ. Near-drowning: consensus and controversies in pulmonary and cerebral resuscitation. *Heart Lung* 1987; **16**: 474–82
2 Howell MA, Guly HR. Near hanging presenting to an accident and emergency department. *J Accid Emerg Med* 1996; **13**: 135–6
3 Mant AK. *Taylor's Principles and Practice of Medical Jurisprudence*. Edinburgh: Churchill Livingstone, 1984
4 Fischman CM, Goldstein MS, Gardner LB. Suicidal hanging: an association with adult respiratory distress syndrome. *Chest* 1977; **71**: 225–7
5 Van der Krol L, Wolfe R. The emergency department management of near-hanging victims. *J Emerg Med* 1994; **12**: 285–92
6 Cooke CT, Cadden GA, Margolius KA. Death by hanging in Western Australia. *Pathology* 1995; **27**: 268–72
7 McHugh TP, Stout M. Near hanging injury. *Ann Emerg Med* 1983; **12**: 774–6
8 Samarasekera A, Cooke C. The pathology of hanging deaths in Western Australia. *Pathology* 1996; **28**: 334–8
9 Dopta BK. Studies on 101 cases of death due to hanging. *J Indian Med Assoc* 1965; **45**: 135–40
10 Shirai S, Tomono Y, Owada T, Maki Y. Traumatic thrombosis of the internal carotid artery: report of three cases due to head injury with basal skull fracture. *No Shinkei Geka* 1976; **4**: 605–10
11 Kraejewski LP, Hertzer NR. Blunt carotid artery trauma. Report of two cases and review of the literature. *Ann Surg* 1980; **191**: 341–6
12 Mears GD, Leonard RB. Blunt carotid trauma: a case report. *J Emerg Med* 1988; **6**: 281–4
13 Maiza D, Theron J, Martel B, Coffin O. Acute carotid occlusion: thrombolytic treatment. *J Mal Vasc* 1996; **21** (Suppl A): 83–9

British Journal of Anaesthesia 84 (4): 525–33 (2000)

BJA

COMMENTARY

Watching anaesthetists work: using the professional judgement of consultants to assess the developing clinical competence of trainees†

J. D. Greaves[1] **and J. Grant**[2]

[1]*Department of Anaesthetics, Royal Victoria Infirmary, Victoria Road, Newcastle upon Tyne NE1 4LP, UK.*
[2]*Joint Centre for Education in Medicine, 33 Millman Street, London WC1N 3EJ, UK*

One of the responsibilities of a consultant is to identify the clinical competence of trainees by observing them at work. The attributes of clinical competence in anaesthesia were defined by interviewing a group of consultants and trainees. Observation of practice was believed to be important in monitoring competence and the supervising consultants all believed that they could recognize competent performance. The account of the structure of observation provided by the anaesthetists is used as the basis of advice on how to conduct an assessment of trainees' developing professionalism by use of the specialist's professional judgement.

Br J Anaesth 2000; **84**: 525–33

Keywords: anaesthesia, assessment; education

Accepted for publication: August 14, 1999

Valid and reliable methodology for assessing the knowledge and skill of doctors is available in most fields of medicine.[1] Less work has been done on possible means of assessing their performance in the total professional task. Clinical outcome is a poor measure of professional effectiveness because it is affected indirectly by so many factors other than the performance of the doctor.[2] In addition, unsophisticated decision-making and clumsy practice may not much alter the ultimate outcome for the patient. Clinical practice can be evaluated by observation even though to date there has been little advice as to how such observations should be made.[3] The need to develop methods of integrated observation of clinical encounters is being recognized as an important facet of the assessment of performance.[4] The purpose of this work was to examine how specialists assess the total professional performance of anaesthetic trainees and to derive a procedure to systematize these methods. Such observations often break down performance into its component parts. Although at a technical level this might be a defensible approach, at the level of professional performance a clinician integrates a range of technical, professional and judgemental skills. It is the integration that marks professional performance and this study is designed to address this directly.

There are a number of reasons why the competence of a doctor in the conduct of clinical practice is difficult to assess.

(1) Clinical reasoning takes place entirely in the doctor's mind and cannot be directly observed. The 'know how' of experts constitutes part of what Michael Polanyi described as tacit knowledge.[5] Tacit knowledge is only seen when an expert uses it Even then, how the expert calls it up and how he wields it is often inexplicable, even to the expert. The objective of this investigation was to discover how doctors use their professional judgement to monitor another doctor's actions.

(2) Clinical questions cannot be framed specifically. In order to construct a traditional test of competence it is necessary to put a question which is sufficiently narrow for there to be a suitably specific answer. Unfortunately it is difficult to frame clinical questions. Can professional judgement be used to interpret the quality of a doctor's decisions without framing specific questions?

(3) There is no agreement about what clinical outcomes are acceptable. There are also few unequivocally correct answers to clinical problems Even superficially straightforward decision-making demands an expert balancing of factors part of which is the expert's judgement as to what is acceptable in terms of outcome.

---

†This paper is accompanied by Editorial II.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Table 1 Membership of the working group

Consultants	12
Regional Advisors	1
Deputy Regional Advisors	4
College tutors	1
Officers of Schools of Anaesthesia	4
Consultants without special responsibility in education	2
Trainees	4
Senior Registrars	2
Senior House Officers	2
Total	16

Method

An expert panel of 16 consultant and trainee anaesthetists met to analyse systematically the assessment of competence by observing practice. The members were drawn from nine Deaneries, worked in a wide range of anaesthetic subspecialties and had a variety of interests in education (Table 1).

The overall approach to data gathering was use of the focused group interview,[6] whereby specific tasks are set for subgroups, and reporting occurs in the plenary with a lead interviewer putting specific questions to the group to encourage discussion and evaluation of ideas as they develop. In this instance, a format for the structured discussion was prepared before the meeting and a number of questions were used to direct the enquiry. Examples of situations that frequently arise during supervision and assessment were used as prompts but the framework allowed members to follow their own direction of analysis. For the initial discussion of each topic the members were divided into three subgroups. The organizers listened to the discussions and led the consensus debriefings. The discussions were not tape-recorded but key remarks and ideas were noted verbatim. All the notes and jottings the members made were kept and examined.

The participants were asked to give an account of the methods used by consultant anaesthetists to evaluate the clinical competence of trainees. These methods were then examined for their suitability for use as part of a formal practice observation.

In this way five issues were explored:

1. How do consultant anaesthetists currently assess trainees by practice observation?
2. Can practice observation form the basis of a valid judgement of trainees' competence?
3. What methods are used by consultant anaesthetists to recognize competent behaviour?
4. Can observation of practice be standardized?
5. Is it possible to recognize levels of professional competence appropriate to particular stages of training?

Results

The group addressed the issues with enthusiasm and the approach was systematic. The subdivision of the group of participants allowed an internal check on reliability of the conclusions and the similarity of views suggested such reliability. The congruity of the views of consultants and trainees also suggested validity of the findings. This paper presents the collated and consensus view of the participants. This view is presented as the first stage in a process of developing and testing an assessment of anaesthetists' professional practice by observation of the integrated performance.

How consultant anaesthetists currently assess trainees by observing practice and if observation of practice can form the basis of a valid judgement of trainees' competence

The participants spontaneously combined the first two issues presented for discussion. They were asked to think about how they assessed the competence of a trainee whom they had not met previously. The group agreed that recognition of competence was not based on a single piece of evidence but depended on several concurrent pieces of evidence. This is known as triangulation.[7 8] Four sources of evidence were described: interrogation of the trainee, documentary evidence, interrogation of third parties and observation of the trainee.

Consultants described the sources that influenced their decisions but had no formal framework for organizing the process. They did not know how they decided to weigh strengths against weaknesses, and were even less clear about how they finally came to a course of action. The process of professional judgement of professional performance is extremely complex and influences are dynamic and interdependent.

The group reported, however, that they used observation of practice in the everyday service evaluation of trainees. When asked directly, 'Can you recognize competence by watching?', all consultants and all trainees said they knew they could. One consultant said:

> 'It's what we do We do it all the time. If you want to know if they're any good, you watch what they do.'

It was the belief of these specialists and trainees that the safety of their practice depended on the fact that consultants can tell whether trainees are safe simply by watching them. This skill was, they believed, part of their professional repertoire. Everyone agreed that they would not be happy to supervise a trainee who had not been observed working. They were all happy to accept the observation of their colleagues and would not necessarily personally review the performance of each trainee that they were called upon to supervise.

Interrogating the trainee: briefing

Consultants described how they question a trainee who is new to them. The approach is relatively structured. Trainees are asked about past experience, particularly about its length and content and the amount of supervision. Consultants place a lot of reliance on the fact that a trainee has had previous experience in a relevant area.

Trainees are asked directly what they think they are capable of doing and what supervision they think they need. The consultants felt that a trainee with previous experience of a type of work would understand more clearly where they would need further direct supervision. The consultant will then explain what they expect the trainee to do independently and in what circumstances they must ask for advice. They then ask the trainee whether they are happy with this. In this exchange the trainee and consultant are negotiating their work relationship, and ensuring patient safety and adequate ongoing supervision.

Documentary evidence

There is a variety of written evidence available to a consultant that can help to find the level of competence of a trainee. The employment record of the trainee is useful, as is the evidence of the variety of experience they have had. All trainees must keep a log of patients they anaesthetize and a summary of this will list their experience. The consultants did not find logbooks very helpful and the view was expressed that searching the logbook was too time consuming. A proper summary was not readily available to the working consultants when they needed it.

Most rotations make use of trainee assessment sheets, which consultants complete. These, or a summary, should move to a new hospital with the trainee and be available via the college tutor. No one referred to these. When asked about them directly the consultants agreed that the systems for filling in and circulating such forms were so poor that the information was not available to them when they needed it.

The examination success of the trainee was significant. In the words of one participant:

> 'If they have passed the primary I feel I can rely on them to look behind events to see what is causing them ... the physiology .. I think that leads to a safe approach.'

Another opinion was:

> 'It shows they have done some hard work, that they're serious about what they do. It's about attitude and I think if they have concentrated on one area (the books) they will probably have concentrated on another (the practice) '

Interrogation of third parties: vicarious observation

Consultants describe gathering evidence about trainees' abilities from third parties. There is a lot of reliance on informal discussions between consultants. A few participants worked in hospitals where trainees were discussed as part of the departmental business meeting and all consultants agreed that they talked about trainees informally and in particular let colleagues know when they were doubtful about a trainee's abilities. Consultants also noted the remarks of surgeons, nurses, midwives and other knowledgeable observers.

Observation of practice

Having decided what to expect of the trainee, the consultant then observes them working and attempts to confirm this opinion. Consultants made particular reference to what they called the 'attitude' of the trainee. With further discussion it emerged that by this they meant the trainee's general approach to work:

> 'I like to see if they shape up. I like to see them organizing themselves and getting everything sorted out '

Consultants had a very clear idea of assessment by observation and they described what appeared to be a well-established routine that was common to most of them Providing structured supervision seems to be part of the professionalism of consultant anaesthetists.

Reviewing

The group described a process of review that followed the observation of practice. In general, debriefing seems to be undeveloped. It is usually limited to the consultant renegotiating the working arrangements with trainees in the light of what they have seen. It does not routinely include feedback to the trainee that might be helpful in their development.

The trainee's view

The trainees in the group understood supervision in the same terms as the consultants. The senior registrars applied similar systems themselves when they supervised more junior trainees. Trainees recognized the stages the supervisor went through in orientating to a trainee and the trainees co-operated in this process. These trainees were firmly of the opinion that their consultants monitored their experience and abilities and made active decisions on supervision The preoccupation of the trainee was with convincing the consultant that they (the trainee) should be allowed to progress in independent practice:

> 'I like to get on, to do new things and have more responsibility. It's sometimes difficult because I want to try something myself but I know I have to tell my consultant and then they tell me what to do. It's difficult to check without getting help.'

This and similar observations by trainees shows that they believe the consultant is engaged in an active process of supervising what they do. They see that it is their responsibility to call for assistance, but they do not describe a supervision process that only reacts to a request for help.

Trainees were as concerned as consultants to get the level of supervision right:

> 'I don't want my consultant to get the wrong idea about me. I don't want to impress him with my competence and then find myself asked to do things I can't do When I need help I need help!'

Again there is the theme of co-operation in making assessments.

What methods do consultant anaesthetists use to recognize competent behaviour?

The consultants believed they already used practice observation successfully to judge the professional competence of trainees. They were able to describe factors that they believed helped make such assessments valid and reliable.

Multiple observations on multiple occasions
All participants felt that single observations of trainees were inadequate for making a good assessment. All agreed that repeated observation by different observers in different situations was required both for fairness and for reliability.

> 'I don't think you should make your mind up about a trainee at the end of one list and even if I am worried about them after I've seen them a few times I like to ask around to see if other people agree with me.'

This approach has support in the instrument literature.[1] Several participants proposed the view that trainees have a complex mosaic of abilities and that the level of competence in one area cannot be predicted from competence in another.

> 'I have a trainee who is very good in most areas but doesn't communicate properly with surgeons. He gives good anaesthetics but he doesn't seem to see that sometimes he has to let the surgeon know what's going on. I don't know whether this really affects the way things go but the surgeons do complain that he keeps them in the dark.'

The consultants were concerned about the problem of being able to make consistent observations of a trainee. Departmental work practices usually made that difficult and there was a feeling that this stopped them doing the job of sizing up a trainee as well as they might.

Patterns of trainee behaviour
Supervisors described patterns of behaviour that keep recurring in trainees. They believed that such patterns could help them recognize trainees with problems. They see professional traits that can lead to difficulty.

> 'Some trainees don't adapt to circumstances. They tell you what their plan is and then they stick with it even when they have good evidence that they should change tack. Sometimes they are slow to respond. They keep trying a treatment that has failed when they should be thinking of something new.'
> 'They focus on the figures. They are always adjusting things when overall it's OK and the patient needs leaving alone. They are worst when they come from an ITU term!'
> 'Sometimes they don't see what's happening. It's quite clear that things have changed. You can tell from across the theatre that the relaxant is wearing off. The trainee is paying attention but they don't notice.'

It seemed that patterns of inappropriate behaviour were more recognizable than patterns of good behaviour, which is a vital point for any system of assessment based on observation.

Active observation
Another issue on which there was general agreement was that simple observation was not enough. One consultant said:

> 'I get the trainee to tell me what they intend to do. I then discuss some ground rules, some limits, within which I will not interfere Then I watch how it goes. If the thing doesn't go as he planned I try and decide if that's because things got out of control. I don't interfere if I can avoid it.'

With this technique the supervisor was comparing observed behaviour with expected behaviour and then trying to draw conclusions about the degree of control the trainee was exerting. This briefing process also allows the supervisor to discover whether the trainee has anticipated likely problems and whether they have contingency plans for such difficulties if they arise.

Supervisors would like their trainees to explain their actions as they go along. This is not a natural thing to do, so the consultant falls back on asking the trainee questions. Questions are pitched at the levels of analysis, synthesis and evaluation:

> 'What's going on there?' 'Why do you do that?' 'What would you do if . .?' 'Is there an alternative approach?'

The consultants ask questions whenever they feel the trainee may not be acting rationally.

Observation of critical events
Another point made by all participants was that watching a trainee's behaviour in the face of certain key events could help the supervisor make good judgements about competence. Good consultant teachers will pay attention to the trainee at these times.

> 'I do anaesthetics for neurosurgery. The trainee should be paying ... have taken good measures to keep the ICP down at key times. He should be watching the blood pressure when the surgeon starts to drill the head. If he's not watching I can see that easily.'

Where there are guidelines for dealing with critical events they form a framework for observation. If the trainee is not observing the rules he may not know or understand them.

The methods used by consultant anaesthetists to recognize competent behaviour

There was immediate agreement that consultants could easily recognize lack of competence when this was bad enough to lead to irregularities in the conduct of anaesthesia. Lack of skill would be easy to see. Lack of knowledge or poor judgement would lead to incorrect actions. Incompetence is easier to see than competence. The incompetent anaesthetist would make clinical judgements that the consultant observer found irrational.

The group believed that some trainees were just competent enough to keep the anaesthetic progressing satisfactorily but had problems that led to a constant risk of complications; then the trainee was not really in control. A lot of discussion centred on this problem and how a situation that is out of control can be spotted. Consultants felt that they were able to see evidence of latent incompetence.

> 'Sometimes a trainee pays a great deal of attention to the monitors and stops paying attention to the patient, they are not paying any attention to what the surgeon is doing—even when important things are happening. I feel that this sort of behaviour is inappropriate.'
>
> 'It's sometimes easy to predict that there may be going to be a problem and the prudent thing is perhaps to take some precaution such as drawing up drugs or checking that blood is available. I feel uneasy if the trainee isn't seeing potential problems.'
>
> 'Even when things are really on an even keel a trainee may be doing something that shows you he still feels very insecure ... He may be checking the tubes of the ventilator and fiddling with it at a time when I can't see any cause for concern. If he thinks there's a problem when there isn't one, what is he going to do when things go wrong? Will he notice?'

Trainees admit to problems

It was recognized by both consultants and trainees that the trainees themselves play a role in monitoring their own competence. The supervisors expect the trainee to tell them when they are unsure of what to do and they say that they keep asking the trainee if they are in control. The trainees similarly believed that they should always tell their consultant when they were unsure of themselves.

A disordered approach to anaesthesia

Several participants expressed the belief that messy, untidy practice that looks disorganized often indicates that the trainee has lost control of the situation.

> 'If they are worrying about the airway or the blood pressure, they forget to keep moving forward with other things like changing the i.v. bag. If things seem to be going to pot I think the registrar has got his mind on a problem. I may not be able to see it because it's not a real problem but it's a good clue to start looking for where he's concentrating.'

There was agreement amongst the consultants that competent practice was recognizable as orderly and progressive. There would always be evidence of control and the anaesthesia and surgery would be moving forward together towards a conclusion. Trainees would show a variety of qualities in their practice and many of these could be observed and recorded as part of an assessment. It was felt that competent practice would include vigilance and appropriate, timely adjustments to the conduct of anaesthesia.

A theme that recurred was how control can be lost and matters can be running out of control without any change in the patient's vital signs.

> 'If the patient has bled unexpectedly the anaesthetist should have a plan. He should have fixed to get some blood ready, even if it's not needed yet. Maybe the crunch will come if they bleed again. Even if they don't he's still been incompetent if he's not got ready for it. Competent people always have a safety net. They have always planned a way out. Sometimes they get upset about the bleeding and you can see them fiddling with the drip or sending the ODA for a central line ... but they forget to get blood. That's disorganized. That's incompetence.'

Table 2 The qualities on which competent practice is based

Knowledge	Anticipation
Skill	Organization
Perception	Flexibility
Confidence	Responsiveness
Prudence	Good manner
Vigilance	Assertiveness
Fluency	Good management
Decisiveness	Good communication

Another consultant pointed out that competence depended on the challenge presented:

> 'An experienced reg. might do well all the time if you just watch. We'd expect him to handle a cardiac arrest but we will never know unless one happens and it usually won't. Watching in theatre can never be the full test but I really think you can tell pretty well who won't cope with the emergency if you watch them enough.'

Experienced supervisors looked for signs of impending disaster in matters of general conduct. Once again this showed a high degree of sophistication in the way supervisors make judgements about learners. The demeanour of the anaesthetist would also help to indicate whether he was in control. Anger and argument might indicate poor communication skills but could also be a sign that the trainee was feeling stressed.

Can observation of practice be standardized?

The group was asked to compile a list of the features that characterize good professional practice. Knowledge and skill were rapidly identified as being different from the other qualities. This was not surprising, as they are entire fields of learning as defined by conventional taxonomies of learning objectives.[9] The group did not feel that testing knowledge was appropriate to a theatre assessment. Knowledge could be measured better by other means such as multiple choice questions (MCQs) and objectively structured clinical examinations (OSCEs). It was agreed that observation would reveal whether a trainee's decisions were consistently based on a secure foundation of knowledge. The question to be considered in watching trainees work is not if they know all about the issues but if their decisions show appropriate use of knowledge and understanding. This aspect of knowledge was very important to observation of practice.

Similarly it was felt that skills could be tested by observation but that such testing should be separate from the overall competence-testing under discussion. Testing of skills was felt to call for a structured observation either at work or by simulation with the tasks being broken into their components. This disrupted normal working patterns so that concurrent assessment of overall judgement would be impossible. Sixteen attributes of competent practice were defined by the team. These are

Table 3 An inventory of the characteristics of anaesthetic practice

Quality and definition	Lack of necessary quality of behaviour	Appropriate behaviour	Over-expression of the quality of behaviour
Knowledgeability: appropriate understanding	Ignorant: decisions are not based on sound understanding; holds mistaken opinions of facts	Practice is based on a sound understanding of principles and facts	[not recognized]
Skill: assurance in performing practical tasks	Unskilful: clumsy; ham-fisted, rough, will undertake procedures without having attained expertise	Shows fluency and expertise in performing practical procedures	[not recognized as a problem]
Perceptiveness: noticing events as they occur	Unobservant: shows delay in noting important events and understanding their significance	Notices important events immediately and realizes their significance	Lacks discrimination in perception: notices minor events and over-emphasizes their significance
Confidence: the assurance with which work is conducted	Under-confident: reluctant to perform tasks within his competence because of lack of understanding of his own abilities	Assesses situations and having identified the necessary abilities to carry out a task and compared them with his own, will carry on if appropriate	Over-confident: attempts tasks beyond his capability by failing to match his own abilities to those required by the clinical situation
Prudence: taking care	Reckless: proceeds directly to action without thoroughly evaluating the situation	Evaluates situations with assurance, identifies hazards, draws up escape routes and institutes prompt action when indicated, knows his own limits	Over-cautious: fails to take appropriate action because of inaccurate perception of relative risk
Vigilance: keeping alert for problems	Inattentive: does not observe clinical problems often enough; does not notice when problems may be arising, slow to respond to signs of trouble, unobservant, easily distracted	Regularly reassesses the clinical situation; always alert to the possibility of difficulty, notices problems swiftly	Over-watchful: over-attentive to inconsequential detail; pernickety, too fussy; allows the search for problems to hinder the progress of anaesthesia and surgery
Anticipation: thinking and planning ahead	No anticipation: does not plan for impending problems; does not see the possibility of trouble until it arrives; does not look ahead to anticipate events; often surprised by events	Realistically evaluates impending difficulties, looks ahead and anticipates the consequences of present events	Sees too much: constantly and unrealistically expects serious problems, always on the edge of his seat
Flexibility: being prepared to change a planned course of actions when necessary	Rigid: does not change plans when presented with evidence that demands this	Constantly re-evaluates decisions as new evidence is presented	Changeable: keeps changing his mind without good reason
Responsiveness: sensitivity to what is going on around	Unresponsive: does not respond appropriately to situations or communications, seems isolated from events, not part of the team	Takes note of what is going on in the operating theatre, integrates properly into the theatre team; attends to what is happening and acts when needed	Always fiddling: responds to all communication, relevant or not; easily distracted, wants to do everyone's job as well as his own
Fluency: progression and continuity of decision-making and practical procedures	Hesitant: having decided on a course of action the trainee is hesitant in carrying it out; a vague vacillating performance, dithering	The work makes consistent smooth, careful progress; skilful, dexterous	Showy: skilful and slick at the expense of care and caution, a showman
Decisiveness: ability to take timely, purposeful action	Indecisive: cannot make up his mind, slow to respond to cues because he cannot decide on a line of action	Makes good decisions after proper consideration of alternatives	Quickly proceeds to action without full consideration, jumps to the first course of action that occurs to him
Communicativeness: ability to articulate ideas and intentions to others	Poor communication: fails to communicate even when the clinical situation demands it; conveys muddled information	Identifies priorities in communication, conveys information in a relevant, clear and concise way	Over-voluble: communicates everything; distracts colleagues from their tasks by inappropriately offering information

Table 3 Cont.

Quality and definition	Lack of necessary quality of behaviour	Appropriate behaviour	Over-expression of the quality of behaviour
Organization: ability to maintain system and order	Disorganized: rushes about without making progress; no system, jumbled, muddled, does not plan	Shows a systematic approach, orderly; planned	Fanatical about organization; rigid organization in minute detail, gets bogged down in planning
Manner: conduct of personal relationships during work	Un-mannerly: disregards the feelings of others; insensitive, rude	Behaves in a manner that is acceptable to colleagues and patients	
Assertiveness: ability to take the lead	Under-assertive: does not make his presence felt; not in command in a crisis; does not give a lead	Firm and disciplined in command; understands where to take a lead and is comfortable in that role	Over-assertive: bossy; disruptive; aggressive; more concerned with keeping other people out of what he sees as his business than with co-operating to get a good job done
Management skills: capacity to organize work and lead a team	Disorganized: does not organize others as a team; fails to organize the work	Plays an appropriate part in planning and managing work	Over manages: concentrates on organization at the expense of practice; does everyone else's job

Table 4 A routine for supervision

Preparatory discussion
Observation of work
Trainee commentary
Interrogation
Review
Scoring

listed in Table 2. The characteristics of each trait were described along with a statement of appropriate behaviour in the relevant domain. Statements of the related inappropriate behaviours were also defined (see Table 3).

The consultants did not claim that their current practice was as structured as this format, indeed for the most part they were not able to explain what factors they used in coming to their judgements. Nonetheless, this list of behaviours was felt to encompass all the attributes of practice about which it would be possible to make a judgement by watching a doctor work, and about which judgements can be made in one way or another. All the consultants used some or all of these methods of making observations.

Is it possible to recognize levels of competence appropriate to particular stages of training?

The group felt that the general nature of the assessment meant that the statements defining level of competence were determined by the experience of the trainee. They dismissed the idea of 'bench-marks' of performance that were relevant to stages of training. The participants all believed that consultants knew what standard to expect of a trainee relative to their experience. They believed that the checklist of behaviours could be applied at any stage of training with equal validity. The list of qualities was considered to be general enough to allow the scheme to be applied to a variety of tasks and in a variety of situations.

A strategy for assessment

It is now possible to put together a strategy for making a professional judgement of a trainee anaesthetist. There are a number of elements in the process (see Table 4).

(1) The consultant should discuss the work with the trainee. The trainee should be asked to summarize what he intends to do. The consultant should give consideration to whether the trainee has planned the work properly and whether he has foreseen any difficulties. The trainee's intentions are a framework against which to judge any decisions he makes. The consultant should ask the trainee if there are aspects of the work about which they are not happy. The trainee and consultant should agree the circumstances in which the consultant will intervene. Such intervention does not invalidate the assessment.

(2) The work is observed. Particular attention is paid to the trainee's method when approaching the times of high work intensity. These times, when there are predictable episodes of clinical decision and judgement, provide good opportunities for assessment. The consultant notes examples of good and bad practice during the work. At the end of the session these are then used as the basis for discussion with the trainee.

(3) The trainee should be asked to explain what he is doing as he goes along. This allows a better analysis of his decision-making.

(4) Consultants should ask probing questions from time to time. These should be directed at the skills of synthesis and evaluation. Trainees should be asked to explain their reasons · whenever they have deviated from their plan.

(5) At the end of the work the trainee should be asked to provide an analysis of how things went and a self-assessment. The consultant should discuss the work and provide feedback. They should discuss the examples of good and bad practice that were noted.

(6) Finally the consultant should evaluate the trainee by selecting the phrase from each category that best describes his or her performance. In doing this all the various phases of the assessment should be integrated. As an alternative the trainee could be asked to provide a self-assessment which takes account of the guidance and comments of the consultants. If this were done the consultant would be able to see whether his feedback had been understood and incorporated into the trainee's self-evaluation.

Discussion

There is a tradition, unchanged in its essentials for many decades, of making judgements about trainees and monitoring their progress by watching them work. That there has been no consistent criticism of the work of trainee specialists or of the quality of new consultants suggests that this process is effective and safe. Criticism is, however, directed at the lack of supervision of the trainees and the assumption is implicit that supervision by consultants will raise the quality of the trainees' work.[10] The in-service assessment of trainees is currently part of the professionalism of consultants and is fundamental to the processes of clinical medical education and anaesthetists have been urged to avoid competency approaches to the assessment of performance.[11,12] However, a new vocabulary and assessment framework need to be developed to recognize and incorporate professional judgement as an acceptable part of formal assessment.

It has long been recognized that the views and opinions of master practitioners are an invaluable resource in designing education in their field. The wide use of the Delphi technique bears testament to this. The difficulty lies in obtaining a consensus from experts. The basis of all group technique is that if two heads are better than one then many heads will be even better. Natural group processes allow the development of ideas between individuals of the group. The consultants co-operating with this study were chosen for their wide variety of clinical backgrounds and their experience as teachers and supervisors. They described supervision and assessment in similar terms and believed that it depended upon the same professional judgement that they used when caring for patients.

This investigation confirmed that the process by which consultants develop their opinion of a trainee's competence is complex, drawing evidence from many sources. It has workings which are probably speciality-specific, and which require to be analysed from the inside by those who are skilled in such decision-making.[13] Specialist doctors must themselves develop the methodology for in-service assessment by practice observation.[14]

Consultants do regularly assess the competence of trainees by watching them at work. They believe that their observations are reliable and valid. They believe that the capacity to assess by observation is part of their professionalism. No participant expressed any concern that they could not make proper assessments of trainees. All the consultant members of the group readily distinguished between tests of knowledge, tests of skill and observations of competence in practice. Professional competence could be assessed in service as part of the professional judgement of the supervising consultant. This group of consultants said that they knew what to expect of a trainee at a given stage of training and that this knowledge was a learned component of their professionalism.

Consultants largely ignore the existing documentary evidence of trainees' competence. They reported that they did not use assessment reports and logbooks as evidence of competence in their routine supervision of trainees. They did place great reliance on their ability to make judgements about trainees through supervision. The consultants described a mechanism they use when supervising which helps them to understand what the trainee is doing (see 'A strategy for assessment' above).

This process was not formal and it did not appear that the consultants put these elements together as a structured observation, nor did they use them all in any particular supervision. The consultants described other procedures that they recognized for increasing the effectiveness of their observations such as watching more carefully at times when the trainee should be responding to predictable problems and noting examples of poor practice. They also recognized patterns of behaviour that suggested the trainee was losing control. An example of this is seen when trainees concentrate on one part of the anaesthetic to the exclusion of others. These elements of structure and organization can be combined to provide a more effective framework for the formal observation of practice.

It is not helpful to the trainee if the consultant cannot explain what is good or bad about their practice. Nor will such a judgement carry weight in the formal process of reviewing training. In recognizing 16 qualities that are common to all practice and which describe all its features, the group provided a framework which can be used to analyse observations. Anaesthetists identified 16 qualities that were displayed in the conduct of competent practice. It is probable that different specialties would generate somewhat different lists. It is not suggested that these qualities of practice make equal contribution to overall competence and there will be many alternative, valid ways of analysing practice. How might such a listing be used in an assessment? If a trainee performs satisfactorily this should be recorded without comment. If the consultant judges that a trainee has failed to perform adequately he or she should decide which of the attributes of competent practice they failed to satisfy. This helps the consultant make constructive feedback and will help the trainee to understand the nature of the criticism that the consultant is making.

In-service assessment by professional observation is a promising development. It formalizes existing workplace-based assessment and has the potential to improve the general structure of teaching supervision. A necessary next step is the submission of large numbers of trainees to this sort of assessment by their supervising consultants during the course of their normal work. This will help to establish the validity and reliability of observations. It is fruitless to compare the consultant's professional judgement of the trainee with any other current assessment as it is unique in focusing principally on the trainee's 'know how' and professionalism. In so doing it directs assessment away from conventional educational measurement and makes the consultant's hard-won clinical competence the arbiter of that of the trainee.

Acknowledgements

Dr Greaves was in receipt of a grant to support this work from the Postgraduate Dean of the Northern Deanery

References

1 Newble D, Jolly B, Wakeford R, eds. *The Certification and Recertification of Doctors. Issues in the Assessment of Clinical Competence*. Cambridge: Cambridge University Press, 1994
2 Grant J, Stanton F. *The Effectiveness of Continuing Professional Development. A Report for the Chief Medical Officer's Review of Continuing Professional Development in Practice*, 2nd edn. London: Joint Centre for Education in Medicine, 1998
3 Jolly B, Grant J. *The Good Assessment Guide*. London: Joint Centre for Education in Medicine, 1997
4 Abouna GM, Hamdy H. The Integrated Direct Observation Clinical Encounter Examination (IDOCEE)—an objective assessment of students' clinical competence in problem-based learning curriculum. *Medical Teacher* 1999; **21**: 67–72
5 Polanyi M. *The Tacit Dimension*. New York: Doubleday, 1967
6 Merton RK, Kendall PL. The focused interview. *Am J Sociol* 1946; **51**: 541–57
7 Cohen L, Manion L. *Research Methods in Education*, 3rd edn. New York: Routledge, 1989
8 Hammersley M, Atkinson P. *Ethnography: Principles in Practice*. New York. Routledge, 1992
9 Bloom BS. *Taxonomy of Educational Objectives. Handbook I—The Cognitive Domain*. London: Longman, 1956.
10 Aitken RJ, Thompson MR, Smith JAE, Radcliffe AG, Samatakis JD, Steele RJC. Training in large bowel surgery: observations from three prospective regional United Kingdom audits. *Br Med J* 1999; **318**: 702–3
11 Greaves JD. Anaesthesia and the competence revolution (editorial). *Br J Anaesth* 1997; **79**: 555–7
12 Myerson KR. Can we assess professional behaviour in anaesthetists? (editorial). *Anaesthesia* 1998, **53**: 1039–40
13 Coles C. A qualitative look at practice. A comment on 'Analysis of the clinical behaviour of anaesthetists'. *Med Educ* **31**: 448
14 Fish D, Coles C. *Developing Professional Judgement in Health Care, Learning through the Critical Appreciation of Practice*. London: Butterworth–Heinnemann, 1998.

British Journal of Anaesthesia **84** (4): 534–40 (2000)

Correspondence

Volatile anaesthetics and the atmosphere: atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane

Editor—The paper by Langbein and colleagues[1] contains much useful experimental data on the rates of atmospherically important reactions of volatile inhalation anaesthetics, but there are a number of factual errors that have led to unwarranted and misleading conclusions. In particular, the effects of halothane on the atmospheric environment are overstated by large margins.

The estimate of the total global emissions of the title compounds, at 10 000 tonnes yr^{-1}, (page 67) is too high by a factor of nearly ten. Halothane is by far the most widely used of the halogenated inhalation anaesthetics but the maximum global capacity to produce it is only 1500 tonnes yr^{-1} and actual production must be less than this.[2 3] Perhaps the error stems from the estimate for the number of procedures involving halogenated inhalation anaesthetics. If this estimate were true, one person in 25 of the *global* population would be anaesthetized in this way each year.

On page 70, the experimental methods of Anne Brown and her colleagues are called into question. In fact, in that paper[4] there is a detailed and referenced description of the experimental method that is actually more informative than that in Langbein and colleagues' paper. Brown and colleagues used a flow system, whereas in the work under discussion here the decay of hydroxyl radicals in a static reactor was observed. However, on the assumption that errors in gas kinetic studies almost invariably lead to more rapid rates of reaction, coupled with the expectation that advances in technique and equipment will have reduced variability, it may be reasonable to adopt Langbein and colleagues' results. Unfortunately, the lifetimes calculated in the paper from those results are seriously in error.

A value of 4.5×10^5 molecules cm^{-3} is used in this paper as the average ground level atmospheric concentration of OH radicals. This is half the normally accepted figure. As discussed extensively in the latest Scientific Assessment of Ozone Depletion,[5] the value that should be used is 9.7×10^5 molecules cm^{-3}.[6] Applying this number to the rate constants derived in Langbein's paper and using the method described by Prather and Spivakovsky,[7] the true values for the lifetimes of the compounds of interest are: halothane, 3.6 yr (reduces to 3.5 yr with the stratospheric loss process); enflurane, 4.5 yr; isoflurane, 3.2 yr; desflurane, 12.3 yr; sevoflurane, 2.0 yr.

Regarding the Ozone Depletion Potential (ODP), equation 12 gives an incorrect formulation. What is actually shown is the equation for equivalent chlorine loading potential (CLP) which corresponds to equation (VI) of Brown and colleagues' paper.[4] To quote that paper: 'The relative importance of the active halogenated species in destroying ozone is altitude-dependent[8] because some of the halogenated compounds are photodissociated at shorter wavelengths than others. The vertical distribution of the compounds and of the solar flux have to be considered in the model calculations. The consequence is that ODP and CLP are different, being related by a chlorine effectiveness factor (CEF) defined as

$$\mathrm{ODP} = \mathrm{CLP} \times \mathrm{CEF} \quad \mathrm{(VII)}$$

CEF depends on photolysis and, using the values in Table 2 of Langbein's paper, halothane will have an effectiveness factor similar to that of CFC-12 (about 0.7), while the factors for enflurane and isoflurane will be closer to that of HCFC-22. Brown and colleagues quote 0.25 and 0.35, respectively, and these values would seem entirely reasonable. Thus the ODP value calculated for halothane on page 70 and quoted in Table 3 is an error because of an incorrect lifetime and inappropriate formula were employed. A more realistic value would be 0.6.

The calculation to derive the effect of halothane described on page 71 is, at best, a crude approximation. As used here, it is wholly misleading. Realistic values for the lifetime of halothane and for the quantities emitted, used in the analytical expression to derive concentration from atmospheric lifetime, show the concentration of halothane at the tropical tropopause (i.e. in the air flow into the stratosphere) to be 0 12 ppt. Using the same value for α as Langbein and colleagues, the chlorine equivalent of this concentration is 6 ppt, compared with a total equivalent chlorine of 4600 ppt.[5] Thus slightly more than one eighth of one per cent of the reactive halogen transported into the stratosphere is accountable to halothane; very different from the 1% calculated in the paper.

As for Global Warming Potentials (GWP), the authors show that the GWP weighted fluxes from these anaesthetics, even using their inflated figures, are small. More realistic values would make them even smaller.

Finally there are two relatively minor points where the paper misleads. The impression is given in the opening discussion that any medical application is an 'essential use' in which CFCs may be used without restriction. The fact is that each year every country that wishes to make use of the derogation has to apply to the Parties to the Montreal Protocol for an essential use allowance, stating the exact quantity (which must not be exceeded) and the exact use. Not all applications are granted.

There is also an underlying assumption in the paper that only halogenated anaesthetics impact the ozone layer or are greenhouse gases. It is worth noting that nitrous oxide has a long atmospheric lifetime (120 yr), is the major non-halogenated ozone-depleting substance with an ODP calculated to be 0.15, and is also a significant greenhouse gas with a GWP referenced to carbon dioxide of 360, or about one tenth that of CFC-11.[5]

This paper contains well conducted practical determinations of important reaction kinetic parameters that are of clear value to atmospheric science. It is a pity that it is marred by inappropriate other data which misleads the reader.

A. McCulloch
ICI Chemicals and Polymers Ltd
Runcorn, UK

1 Langbein T, Sonntag H, Trapp D, Hoffmann A, Malms W, Roth E-P, Mors V, Zellner R. Volatile anaesthetics and the atmosphere. atmospheric lifetimes and atmospheric effects of halothane, enflurane, isoflurane, desflurane and sevoflurane. *Br J Anaesth* 1999; **82**: 66–73

2 McCulloch A. Mechanisms of atmospheric degradation of HCFCs and HFCs and formation of trifluoroacetic acid. In *Workshop on the Environmental Fate of Trifluoroacetic Acid*, March 3–4, 1994, Miami Beach, FL. Alternative Fluorocarbon Environmental Acceptability Study, Washington, 1995

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

3 Boutonnet JC, Bingham P, Calamari D, et al. Environmental risk assessment of trifluoroacetic acid. *Human Ecol Risk Assess* 1999; **5**: 59–124

4 Brown AC, Canosa-Mas CE, Parr AD, Wayne RP. Laboratory studies of some halogenated ethanes and ethers. measurements of rates of reaction with OH and of infrared absorption cross sections. *Atmos Environ* 1990; **24A**· 2499–511

5 Albritton DL, Aucamp PJ, Megie G, Watson RT. *Scientific Assessment of Ozone Depletion. 1998*, World Meteorological Organisation Global Ozone Research and Monitoring Project Report No 44, WMO, Geneva, 1999

6 Prinn RG, Weiss RF, Miller BR, Huang J, Alyea FN, Cunnold DM, Fraser PJ, Hartley DE, Simmonds PG. Atmospheric trends and lifetime of CH_3CCl_3 and global OH concentrations. *Science* 1995; **269**. 187–92

7 Prather M, Spivakovsky CM. Tropospheric OH and the lifetimes of hydrochlorofluorocarbons. *J Geophys Res* 1990; **95**· 18723–9

8 Wayne RP. *Chemistry of Atmospheres*, Oxford University Press, 1985; 156

Editor—There are a number of results and conclusions in our paper which have been criticized by Dr McCulloch. Our responses to these criticisms are:

(i) The first point refers to our estimation of global emission of volatile anaesthetics. The number cited in our paper (10 000 t yr^{-1} globally) is a simple estimate based on an extrapolation of the number of inhalation anaesthetics performed in Germany. Certainly, this method of extrapolation is not very satisfactory but it was impossible to obtain more detailed information from the producers of volatile anaesthetics at the time of writing the paper. The input data for our estimations are given. It is correct that the global number of inhalation anaesthetic applications is the most uncertain quantity, but with respect to the corresponding number for Germany and with the intention of producing an upper limit, this extrapolation seemed reasonable. In our opinion it is just as approximate as McCulloch's statement of a maximum global capacity of halothane production of 1500 t yr^{-1}. This figure must be limited to the so-called reporting countries and may well exclude some production elsewhere. Furthermore, it is questionable whether or not halothane is still the most widely used halogenated inhalation anaesthetic. Halpern has published relative market share data which show a continuous reduction in relative halothane consumption from 1973 to 1989 in the USA and Europe.[1] Accepting this result McCulloch's 1500 tonnes yr^{-1} halothane production capacity represents only 15–25% of the annual number of halogenated anaesthetics, suggesting a total production of all of these substances of between 6000 tonnes yr^{-1} and 10 000 tonnes yr^{-1}, not significantly different from the figure quoted in our paper.

(ii) McCulloch's statement that we question the experimental method of Brown and colleagues is not correct. We stated that their article gave no experimental details. However, we are aware that the flow system study of Brown and colleagues is equally suitable for generating reliable rate data. Nevertheless, differences between Brown and colleagues study and our study are well encompassed by the absolute error limit of any absolute rate study of fast gas phase reactions. Since the likelihood of measuring too fast reaction rates is considerably higher than measuring too low rates, the lower rate coefficients (as determined in our work) are usually given preference. This is also acknowledged by McCulloch.

(iii) The third concern raised by McCulloch is the average ground level atmospheric concentration of OH radicals used in the derivation of atmospheric lifetimes. At the time of writing our paper the accepted value of this concentration was the one which we used in the calculations. Meanwhile this value has increased by almost a factor of two. By implication, an increased OH concentration produces a lower atmospheric lifetime of all chemicals which are primarily degraded by OH, including the volatile anaesthetics. Therefore, on the basis of the globally averaged OH concentration alone it might appear justified to reduce the atmospheric lifetimes.

(iv) Equation 12 of our paper is said to provide an incorrect formulation for the ozone depletion potential-ODP. We are aware of the fact (and we have stated this in the appendix of our paper) that ODP values are obtained from model calculations of the total depletion of column ozone by compound X relative to CFC-11. Although the formula used in our paper is indeed an 'effective chlorine loading potential' it is entirely sufficient for an approximate estimation of ODP. More precise derivations should in our view not be attempted without reference to a detailed modelling study. The corrections suggested by McCulloch point qualitatively in the right direction but should not be considered as being quantitatively correct.

(v) We agree with McCulloch that the calculation to derive the effect of halothane on the atmospheric environment is, to a certain extent, approximate. This is due to remaining uncertainties in our primary data (rate coefficients, absorption spectra) as well as their derived quantities (chemical and photochemical lifetimes). The most crucial data with respect to the atmospheric burden of volatile anaesthetics is their atmospheric concentration, which is intimately related to the quantities produced and/or emitted. The question of what fraction of these compounds enters the stratosphere and destroys ozone cannot reliably be answered without detailed modelling studies. However, it should be borne in mind that again the net emission quantity is the most relevant with respect to total impact.

(vi) Similar arguments as for the ODP apply to the greenhouse warming potential (GWP) values. However, these factors are only dependent on atmospheric lifetimes (and infrared band strength). Detailed information on GWP again requires radiative transfer model calculations. The approximation used in our paper (which is not criticized by McCulloch) is entirely sufficient since the contribution of volatile anaesthetics to total tropospheric warming is negligible.

(vii) Montreal Protocol: it is correct that even within the Montreal Protocol the so called essential uses of halogenated compounds is subject to regulations. Annual productions must be applied for. This also applies to CFCs such as those used in inhalation sprays

(viii) We are well acquainted with the atmospheric burden of nitrous oxide. This compound was not included in our investigations since its lifetime and its atmospheric chemistry are well documented. Moreover, the natural sources of this gas are so legion that it appears to be a purely academic question as to how much of it is released into the atmosphere by medical applications.

In summary, we believe that the comments on our manuscript made by McCulloch have justification primarily with respect to our choice of the ambient atmospheric concentration of the hydroxyl radical. The quantity chosen in our paper was the one accepted in the literature at the time of writing. The other problems addressed by McCulloch require further evaluation especially estimation of the production and emission numbers of volatile anaesthetics as well as the more detailed modelling studies of their ODP values.

T. Langbein[1]
H. Sonntag[1]
D Trapp[1]
A. Hoffmann[2]
W. Malms[2]
E -P Roth[2]
V Mors[2]
R Zellner[2]
[1]*Department of Anaesthesia*
Georg-August-Universität
Göttingen, Germany
[2]*Institute for Physical and Theoretical Chemistry Universitat-GH-Essen, Germany*

1 Halpern DF. Fluorinated inhalation anaesthetics. In: Banks RE, Smart BE, Tatlow YC, eds. *Organofluorine Chemistry, Principles and Commercial Applications*. New York and London: Plenum Press, 1994.

Oxygenator exhaust capnography as an index of arterial carbon dioxide tension during cardiopulmonary bypass using a membrane oxygenator

Editor—We were interested in the paper by O'Leary and colleagues[1] who found oxygenator exhaust capnography during cardiopulmonary bypass was not useful for estimating the arterial carbon dioxide tension (Pa_{CO_2}).

The authors hypothesized that it would be important to temperature correct their data. Unfortunately, they used nasopharyngeal temperature which may not be the most appropriate; the temperature of the blood at the point that carbon dioxide is being evolved may be more logical. This is not difficult in practice, the temperature of arterial blood at the oxygenator outlet is (or should be) routinely measured during cardiopulmonary bypass.

To test our hypothesis we observed 19 patients undergoing nonpulsatile hypothermic (28°C) cardiopulmonary bypass using a Terumo Capiox SX membrane oxygenator and a Criticare POET IQ capnograph, taking 38 samples during cooling and rewarming, and using Dr O'Leary's method with one modification—blood gases were corrected to the temperature of arterial blood rather than nasopharyngeal temperature.

The 95% limits of agreement between temperature corrected Pa_{CO_2} and partial pressure of CO_2 in the oxygenator exhaust gas (PE_{CO_2}) was −0.54 kPa to +0.78 kPa. The coefficient of determination between temperature corrected Pa_{CO_2} and PE_{CO_2} was 0.95 (Fig. 1). There was a tendency for PE_{CO_2} to under-read during hypothermia (Fig. 2). Of interest, when blood gases were corrected to nasopharyngeal temperature, the 95% limits of agreement were −2.97 kPa to +3.0 kPa which is an inaccuracy similar to that described in O'Leary's paper.

These observations suggest that oxygenator exhaust capnography may allow real-time, continuous estimation of Pa_{CO_2} with clinically useful accuracy, provided that it is corrected to arterial blood temperature, not the temperature of the nasopharynx.

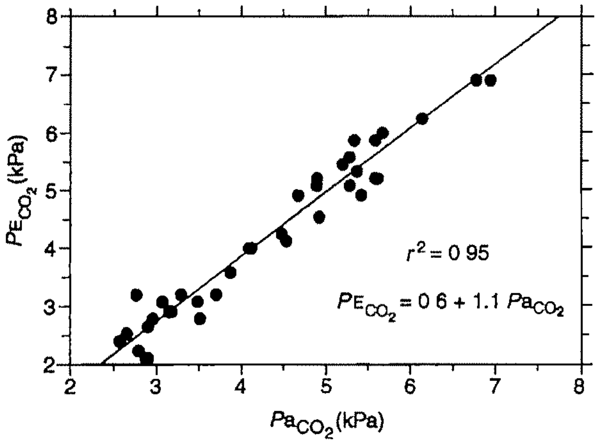


Fig 1 Relationship between the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) and the partial pressure of carbon dioxide in oxygenator outlet exhaust (PE_{CO_2})

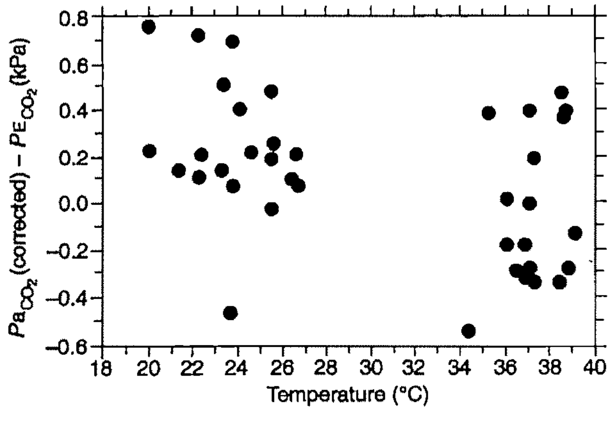


Fig 2 Relationship between arterial blood temperature and the difference between the partial pressure of carbon dioxide in arterial blood (Pa_{CO_2}) and the partial pressure of carbon dioxide in oxygenator outlet exhaust (PE_{CO_2}).

W. M. Weightman
M. R. Sheminant
Department of Anaesthesia
Sir Charles Gairdner Hospital
Perth, Australia

1 O'Leary MJ, MacDonnell SP, Ferguson CN. Oxygenator exhaust capnography as an index of arterial carbon dioxide tension during cardiopulmonary bypass using a membrane oxygenator. *Br J Anaesth* 1999; **82**: 843–6

Editor—Thank you for the opportunity to respond to the letter of Weightman and Sheminant, who should be congratulated for rapidly performing their study in response to our paper. As discussed in the opening paragraphs of our paper, we set out to determine whether monitoring exhaust gas carbon dioxide partial pressure (PE_{CO_2}) would be clinically useful during cardiopulmonary bypass; that is to say could measuring PE_{CO_2} take the place of blood gas monitoring? We did not hypothesize, however, that temperature correction of arterial blood gases would improve the agreement between the two measures (Pa_{CO_2} *vs* PE_{CO_2}). Having noted that there was poor agreement with Pa_{CO_2} uncorrected to nasopharyngeal temperature, we then went on to investigate whether temperature correction might improve the level of agreement. We agree that measuring temperature at the point where gas exchange is occurring, rather than in the nasopharynx, is a logical step, and Weightman and Sheminant claim to have obtained reasonable agreement between the two measures when this technique is employed. Although this is clearly of interest, we would disagree with their statement that 'oxygenator exhaust capnography may allow real-time, continuous estimation of Pa_{CO_2} with clinically useful accuracy, . . .' In modern perfusion practice, using alpha stat blood gas correction, the *uncorrected* Pa_{CO_2} is the variable of interest and other measurement methods are only useful if they reflect this value accurately.

We do have a few concerns with the data presented by Weightman and Sheminant, however. Only the relationship between Pa_{CO_2} corrected to either nasopharyngeal or arterial blood temperature and PE_{CO_2} are reported. We would be interested to know the relationship between uncorrected Pa_{CO_2} and PE_{CO_2} in their study—was the agreement between these measures similar to our findings? Plots of the difference between the two measures *vs* the average of the two measures for corrected and uncorrected blood gases using both nasopharyngeal and arterial blood temperature measurements would be informative in a way that Figures 1 and 2 are not. In Figure 2, the relationship between the difference in the two measures (corrected Pa_{CO_2} and PE_{CO_2}) and temperature is shown; why are the hypothermic measures all at very low temperatures (20–27°C) when in the text the cooling temperature is stated at 28°C? Furthermore, why are there apparently 18 measurements in the upper temperature range and 20 in the lower range when 19 patients were studied? The absence of any measurements between 27°C and 34°C, where the majority of our measurements were made, makes comparison with our data, presented in the same format, impossible.

M J O'Leary
Intensive Care
St George Hospital
New South Wales, Australia

S. P. MacDonnell
Anaesthesia and Intensive Care
Colchester Hospital
Colchester, UK

C. N. Ferguson
Anaesthesia and Intensive Care
Derriford Hospital
Plymouth, UK

Perioperative hypotension following plasma volume expansion with albumin in an angiotensin-converting enzyme inhibited infant

Editor—Perioperative hypotension is usually due to hypovolaemia and often requires treatment with plasma expanders. Unfortunately, plasma expanders may themselves cause hypotension.[1] Which, when and how to use plasma expanders is a matter of a continued debate. Historically, the plasma expander of choice in paediatric practice is albumin, and in particular in paediatric renal transplant patients where a poorer graft survival has been demonstrated with synthetic colloids.[2 3]

We wish to report a case of severe hypotension associated with a bolus dose of 4% albumin (Albumex 4% – Commonwealth Serum Laboratories) during anaesthesia in an infant scheduled for a living-related donor kidney transplant.

The infant was a 9.8 kg 20-month-old female with chronic renal failure due to tubular interstitial nephritis. She was on peritoneal dialysis and her medication included captopril 2.5 mg tds, sodium carbonate, calcitriol, pentavite, iron, folate, recombinant erythropoietin, prednisolone, cyclosporin A and mycophenolate. General anaesthesia was induced with thiopental 50 mg, atracurium 8 mg and fentanyl 20 µg. Anaesthesia was maintained with isoflurane 1% in N_2O 50%/O_2. A double-lumen 5 FrG central venous catheter, a radial intra-arterial catheter and a low thoracic epidural (T_{11}/T_{12}) were then inserted. Arterial pressure remained stable at 90–100 mm Hg systolic, with a central venous pressure of 7 mm Hg and a heart rate of 110 beats min^{-1}. The arterial pressure fell to 85–90 mm Hg after establishment of the epidural block with 7 ml of 0.25% bupivacaine over 15 min, with no change in heart rate or CVP. For 35 min while awaiting the arrival of the donor kidney, the patient remained haemodynamically stable. Preoperatively, it had been decided to increase her plasma volume in anticipation of surgery, which involved anastomosis of the donor renal artery and vein to the aorta and inferior vena cava respectively. A bolus dose of 20 ml Albumex 4% was given via the central line over a 2-min period and the arterial pressure fell within 1 min to 50–55 mm Hg systolic with no change in heart rate or CVP.

While excluding other causes of hypotension, 250 ml of normal saline was rapidly infused over 10 min resulting in a slight increase in systolic arterial pressure to 70–75 mm Hg and a rise in CVP to 10 mm Hg. A dopamine infusion of 5–10 µg kg^{-1} min^{-1} was commenced with a return of systolic arterial pressure to 90 mm Hg 10 min later. During the remainder of the operation, fluid management consisted of crystalloids and packed red blood cells neither of which elicited any hypotensive episodes. A further epidural top-up of 0.25% bupivacaine 3 ml at the end of surgery did not result in any change in blood pressure. The child was extubated and transferred to the paediatric intensive are unit for further management. A postoperative chest x-ray did not show any sign of a pneumothorax.

A sample was taken from the albumin bottle (lot no. 3420000083) and analysed for prekallikrein activating factor (PKA) levels at CSL Bioplasma Ltd. The PKA concentration in the albumin solution was found to be 10 IU ml^{-1}, which is less than the highest required limit for release in Australia (<28.6 IU ml^{-1}).

This case report demonstrates that the administration of albumin in children receiving angiotensin converting enzyme inhibitors may produce unwanted hypotension, despite albumin solution PKA levels within manufacturer specifications It was fortuitous that the albumin administration occurred during haemodynamic stability rather than during a period of significant intravascular fluid shifts in which distinguishing the cause of the persistent hypotension may have been difficult.

ACE inhibitors prevent the conversion of angiotensin I to angiotensin II as well as the biodegradation of bradykinin. Albumin solutions contain low levels of prekallikrein activating factor, which activates bradykinin. In the presence of ACE inhibition, the plasma half-life of bradykinin is significantly prolonged, thus administration of prekallikrein activator may result in significant and prolonged hypotension.[4] This effect is, however, unpredictable as plasma ACE levels are highly variable and the amount of bradykinin produced from ACE inhibition may not cause significant hypotension. It has been suggested that a rapid rate of infusion (30–40 ml min^{-1}) of albumin 5%, for example in plasmapheresis, can cause a significant rise in bradykinin levels to produce flushing and hypotension in adult patients taking ACE inhibitors.[5]

Our patient was given her normal dose of captopril the night before surgery. As renal failure can significantly prolong the half-life of captopril, from 2 h up to 40 h,[6] plasma ACE would have been inhibited at the time of surgery. The albumin was also administered rapidly (1 ml kg^{-1} min^{-1}) via a central route and in combination with ACE inhibition may have produced a clinically significant rise in bradykinin level to account for the hypotension.

As albumin solutions are often used to maintain intravascular volume in renal transplantation, it may be prudent to stop the use of ACE inhibitors 24 h prior to surgery (if possible)—or to avoid the use of albumin in patients on ACE inhibitors in order to avoid such adverse reactions.

S. Y Fong
T. G. Hansen
Department of Paediatric Anaesthesia
Princess Margaret Hospital for Children
Subiaco, Perth, Western Australia

1 Walker SR, MacSweeney ST. Plasma expanders used to treat or prevent hypotension can themselves cause hypotension. *Postgrad Med J* 1998; **74**: 492–4
2 Dawidson I, Peters P, Sagalowski A, Abshier D, Coorpender L. The effect of intraoperative fluid management on the incidence of acute tubular necrosis. *Transplant Proc* 1987; **19**: 2056–7
3 Cittaova ML, Leblanc I, Legendre Ch, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996; **14**: 1620–2
4 McKenzie AJ. Possible interaction between SPPS and enalapril. *Anaesth Intensive Care* 1990; **18**. 124–6

5 Owen HG, Brecher ME. Atypical reactions associated with use of angiotensin-converting enzyme inhibitors and aphresis. *Transfusion* 1994; **34**: 891–4

6 Drummer OH, Workman BS, Miach PJ, Jarrott B, Louise WJ. The pharmacokinetics of captopril and captopril disulphide conjugates in uraemic patients on maintenance dialysis: comparison with patients with normal renal function. *Eur J Clin Pharmacol* 1987; **32**: 267–71

Tracheal intubation via the intubating laryngeal mask by inexperienced personnel

Editor—We read with interest the article by Avidan and colleagues[1] on the ability of inexperienced health workers to perform tracheal intubation by using either the conventional blind technique via the intubating laryngeal mask (ILM) or direct laryngoscopy. According to their results, the authors do not support the use of the ILM for tracheal intubation by inexperienced personnel. Our attempts to examine the ability of nurses, inexperienced at advanced airway management, to perform tracheal intubation via the ILM using a light-guided technique, came to a different conclusion.[2]

After ethics approval, six nurses followed a 2-h training programme of light-guided tracheal intubation via the ILM in a mannikin and then each intubated 10 consenting, anaesthetized and paralysed patients, with instruction from an anaesthetist, by using a prototype of an illuminated completely flexible catheter with a bulb attached to its distal end.[3] The device was placed into a straight tracheal tube in such a way that the bulb could be adjusted at the distal end. The tube preloaded with the device was inserted via the ILM and by observing the glow in the neck was advanced into the trachea. The overall success rate of tracheal intubation was 95% (57 of 60). The success rate after two attempts at tracheal intubation was 76% (46 of 60), which is higher than the study of Avidan and colleagues (43%, 38 of 89),[1] $P<0.0001$, odds ratio: 4.4.

Recently, in a preliminary randomized double cross-over study, light-guided tracheal intubation proved to be superior to the conventional blind intubation via the ILM, since it was found to be more rapid and more successful (100% *vs* 91%) when it was performed by anaesthetists.[4] Conventional tracheal intubation via the ILM has the disadvantage of being a 'blind-on-blind' technique, since both the ILM and the tracheal tube are inserted without direct vision of the larynx.[5 6] This problem seems to be more significant in those inexperienced with advanced airway management. Thus we agree with Avidan and colleagues[1] about the difficulties experienced by the participants in their study, either to perform appropriate blind manipulations of the ILM when the tracheal tube cannot pass into the larynx, or to recognize the subtle resistance encountered when the tracheal tube passes blindly into the oesophagus. Light-guided tracheal intubation via the ILM overcomes these disadvantages, since whenever resistance is felt during insertion of a tracheal tube a variety of light-guided strategies are instituted,[2 4 7] depending on the location of the glow in the neck. Additionally, accidental oesophageal intubation can be diagnosed early by noting absence of the glow.[2 4]

Avidan and colleagues[1] wonder why blind tracheal intubation via the ILM was not successful even though the ILM was 'well positioned' by participants in their study. We consider that good positioning is a prerequisite for the ILM to act as a ventilatory device. However, such positioning is not necessarily sufficient for the ILM to act additionally as an aid to successful tracheal intubation. According to our experience in 400 patients, there were 152 cases (38%) with misplacement of the glow in the neck. This glow misplacement was not related to adequate ventilation via the ILM. However, the achievement of successful tracheal intubation needed appropriate light-guided manipulation of the handle of the ILM in order to redirect the glow into the midline at the level of the laryngeal prominence.

We consider that this light-guided technique has advantages in optimizing ILM positioning in the laryngopharynx, and in achieving successful tracheal tube advancement from the laryngopharynx to the trachea. Furthermore, it has the potential for tracheal intubation via the ILM, even by those inexperienced at advanced airway management.

V. Dimitriou
G. S. Voyagis
Department of Anaesthesia
Gennimatas and Sotiria Hospitals
Athens, Greece

1 Avidan MS, Harvey A, Chitkara N, Ponte J. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth* 1999; **83**: 615–7

2 Dimitriou V, Voyagis GS. The use of an illuminate flexible catheter for light-guided tracheal intubation through the intubating laryngeal mask by nurses. *Eur J Anaesthesiol* 1999; in press

3 Dimitriou V, Voyagis GS. Use of a prototype flexible lighted catheter for guided tracheal intubation through the intubating laryngeal mask. *Anesth Analg* 1999; **89**: 257–8

4 Dimitriou V, Voyagis GS. Light-guided tracheal intubation through the intubating laryngeal mask using a prototype illuminated flexible catheter. *Eur J Anaesthesiol* 1999; **16**: 448–53

5 Kapila A, Addy EV, Vergese C, Brain AIJ. The intubating laryngeal mask airway: an assessment of performance. *Br J Anaesth* 1997; **79**: 710–13

6 Dimitriou V, Voyagis GS. Blind intubation through the intubating laryngeal mask airway: What about the accidental oesophageal intubation? *Br J Anaesth* 1999, **82**: 478–9

7 Dimitriou V, Voyagis GS. Unexpected resistance during tracheal tube insertion through the intubating laryngeal mask. *Eur J Anaesthesiol* 1999; **16**: 419–20

Editor—Thank you for the opportunity to respond to the letter by Dimitriou and Voyagis. The technique of light-guided intubation via the intubating laryngeal mask (ILM) is interesting and appears to overcome some of the criticisms of the ILM. There are, however, certain methodological differences which make comparison between the two studies difficult.[1 2]

In their study, training was a 2-h intensive programme, with 10 successful ILM insertions and intubations by participating nurses considered adequate. Each nurse was allowed to intubate 10 study patients using an illuminated catheter and the ILM. Our view was that if training was rigorous and if participants were allowed to intubate many patients, they could no longer be considered novices at the technique. We therefore conducted a brief training comprising only two successful ILM intubations on manikins. Moreover, each participant was restricted to a maximum of five study patients. This approach is reinforced by Dimitriou and Voyagis themselves, who found that participants were more successful in their second five patients.[1]

Statistical comparison between participants' successes in the two studies must therefore be interpreted with extreme caution. Not only the validity, but also the accuracy of the comparisons is questionable. In the Dimitriou study, success was judged cumulatively rather than as a proportion of all attempts. There were 60 first attempts at intubation of which 38 were successful. There were 22 second attempts at intubation of which eight were successful. The success rate they quoted after two attempts was 46/60.[1] This is misleading because it fails to convey the further

22 attempts. It would seem more accurate to report the success rate after two attempts as 46/82. The difference between 46/82 (56%) and 38/89 (43%) (the intubation success in our study after two attempts[2]) is not statistically significant, $P=0.11$ (Fisher's exact test).

A prospective, comparative study between the conventional blind ILM intubation technique and light-guided ILM intubation by inexperienced personnel should be conducted. Pending the findings of such a study, we reserve judgement about the possible superiority of one technique over the other in this context.

M. S. Avidan
A. Harvey
N. Chithara
J. Ponte
Department of Anaesthesia
Kings College Hospital
London, UK

1 Dimitriou V, Voyagis GS. Use of an illuminated flexible catheter for light-guided tracheal intubation through the intubating laryngeal mask by nurses. *Eur J Anaesthesiol* 1999, in press

2 Avidan MS, Harvey A, Chitkara N, Ponte J. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth* 1999; **83**: 615–17

Emergency repair of incidentally diagnosed ascending aortic aneurysm immediately after Caesarean section

Editor—We read the case report by Ecknauer and colleagues[1] with great interest. In particular, it highlights the diversity of approach to induction of general anaesthesia by cardiac and obstetric anaesthetists. This patient posed problems commonly seen by each subspecialty. She was 10 h post-partum following delivery at term and must therefore still be considered at risk of gastro-oesophageal reflux and pulmonary aspiration of gastric contents. She also presented with a large ascending aortic aneurysm for which control of blood pressure on induction was essential. During anaesthesia for Caesarean section, both issues were addressed by performing an epidural block. Induction for aortic repair was with flunitrazepam, fentanyl and pancuronium with the use of an esmolol infusion to aid blood pressure control. Although this fully addresses the requirement for haemodynamic stability, we are concerned that she remained at risk of aspiration. While it is generally accepted that the effects of pregnancy with regard to gastric emptying are rapidly reversed within the first few hours post-partum the patient still remains at risk of aspiration of gastric contents for a significant period into the puerperium.[2]

We believe that some attempt could have been made to reduce the risks of aspiration in this patient by pretreatment with antacids and a degree of modification of the cardiac anaesthetic technique to take into account the potential aspiration risk. A classical rapid sequence induction with a predetermined bolus of thiopental and succinylcholine would clearly not afford the blood pressure control required. However, induction employing either succinylcholine or rocuronium to achieve muscle relaxation rapidly with the concomitant application of cricoid pressure may improve airway safety without adversely affecting haemodynamic stability.

D. A. Jones
P. Sutherland
Ann Arbor
Michigan, USA

1 Ecknauer E, Schmidlin D, Jenni R, Schmid ER. Emergency repair of incidentally diagnosed ascending aortic aneurysm immediate after Caesarean section. *Br J Anaesth* 1999; **83**: 343–5

2 Bogod D. The post partum stomach—when is it safe? *Anaesthesia* 1994, **49**: 1–2

Editor—Thank you for the opportunity to reply to Drs Jones and Sutherland. As they pointed out, we were facing the problem of a patient a few hours post-partum and scheduled for emergency aortic repair with the need for a haemodynamic stability during induction.

Anaesthesia was induced with flunitrazepam, fentanyl and pancuronium and the use of a continuous esmolol infusion to aid control of blood pressure. Although this fully addressed the requirement for haemodynamic stability, Drs Jones and Sutherland are concerned that the patient remained at risk of aspiration. They proposed pretreatment with antacids and an induction employing either succinylcholine or rocuronium to rapidly achieve muscle relaxation.

Unfortunately, we did not describe in sufficient detail the management of the patient in respect of the risk of gastric regurgitation. Prior to delivery, the patient received an antacid (sodium citrate) and an H_2 blocker (ranitidine). In the ICU, where the patient stayed until coming to the operating room for aortic repair, omeprazole was also given. We did not perform a classical rapid sequence induction, but applied cricoid pressure—which we also did not mention—to improve airway safety. Regarding the neuromuscular blocking agents, we prefer pancuronium because of its slight sympathomimetic action and preservation of haemodynamic stability. I agree that rocuronium would have been a suitable alternative. In this case we believe that we had primarily to focus on the potentially fatal risk of aortic rupture caused by haemodynamic deterioration during induction

As we had the ability to treat any aspiration, but would have run the risk of aortic rupture during induction if we had changed our technique, the successful management of our patient makes us believe that we made the right decision.

E. Ecknauer
Division of Cardiovascular Anaesthesia
University Hospital
Zurich, Switzerland

Myocardial ischaemia during Caesarean section

Editor—ST segment changes in the electrocardiograph (ECG) and symptoms such as chest pain and dyspnoea occur in a significant number of patients undergoing Caesarean section under spinal anaesthesia.[1] The relationship of these symptoms to myocardial ischaemia has been obscure,[2–4] although there are reports of patients who had risk factors (family history, smoking or hypertension) developing myocardial infarction or angina pectoris during Caesarean section.[5] We report the case of a healthy subject with no risk factors who developed myocardial ischaemia during Caesarean section.

A 19-yr-old parturient (144 cm, 54 kg) underwent Caesarean section for cephalopelvic disproportion. After preloading with 0.5 litre of lactated Ringer's solution, spinal anaesthesia was performed with tetracaine 9 mg in 1.8 ml of 10% dextrose containing morphine hydrochloride 0.18 mg. Oxygen was administered via a face mask. Ephedrine hydrochloride was injected intravenously five times (4 mg on each occasion) to maintain systolic arterial pressure above 90–100 mm Hg, and atropine sulphate 0.5 mg was injected following a decrease in heart rate to 55 beat min^{-1}. A sensory block was obtained to T4 by the start of the operation.

After beginning the operation, the patient complained of dyspnoea, although the level of block did not change. After delivery of a 3.9 kg baby and the placenta, methylergometrine maleate 0.2 mg was administered intravenously, and prostaglandin $F_2\alpha$ 1000 μg was injected topically for augmentation of uterine contractility. Immediately after administration of these drugs, the heart rate increased, and the systolic arterial pressure rose to 170 mm Hg. Premature ventricular ectopics were observed on ECG (Fig. 1B), which developed rapidly into ventricular tachycardia (Fig. 1C). We gave lidocaine hydrochloride on two occasions i.v. (50 mg each dose), and continued to administer oxygen. Although sinus rhythm was restored after 2 min, ST segment depression occurred (Fig. 1D). We therefore administered isosorbide dinitrate i.v. twice (2.5 mg each dose).

Because of her anxiety and hyperventilation, general anaesthesia was induced with a rapid sequence induction. Isosorbide dinitrate 0.4 $\mu g\ kg^{-1}\ min^{-1}$ was given by continuous infusion. By the end of the operation, the ST segment depression had returned to normal. The patient was transferred to the intensive care unit, and the tracheal tube was removed 30 min later. The plasma concentration of phosphocreatine kinase had increased to 89 IU l^{-1} by the end of the operation (normal range; 1–20 IU l^{-1}), but had almost returned to normal (26 IU l^{-1}) by the next day.

In this patient, premature ventricular ectopics, ventricular tachycardia and marked depression of the ST segment were observed on the ECG. The plasma phosphocreatine kinase concentration only increased transiently. These signs strongly suggest ischaemic cardiac dysfunction. We gave methylergometrine after delivery of the placenta to reduce the incidence and extent of post-partum atony and haemorrhage. This agent has adverse effects such as nausea, vomiting and chest pain, all of which are attributed to smooth muscle contraction. Methylergometrine may have caused the arrhythmias in this patient due to an increased rate pressure product and coronary artery vasoconstriction. Administration of prostaglandin $F_2\alpha$ may also have contributed to the cardiac dysfunction.

However, these factors, even in combination, are unlikely to cause myocardial ischaemia in a patient without risk factors. Since the patient had signs of hypovolaemia (hypotension and bradycardia) after administration of the spinal anaesthetic, for which we administered ephedrine and atropine, this may have contributed to the abnormal cardiac function. High spinal blockade may depress cardiac function by decreasing myocardial contractility. Electrolyte imbalance caused by hyperventilation is also a possible precipitating factor.

In conclusion, various factors that increase myocardial oxygen demand and decrease oxygen delivery during Caesarean section may cause myocardial ischaemia even in patients who have no risk factors.

R. Ozaki
N. Adachi
T Yorozuya
T. Nagaro
T Arai
Department of Anesthesiology and Resuscitology
Ehime University School of Medicine
Shitsukawa, Shigenobu-cho
Onsen-gun, Ehime, Japan

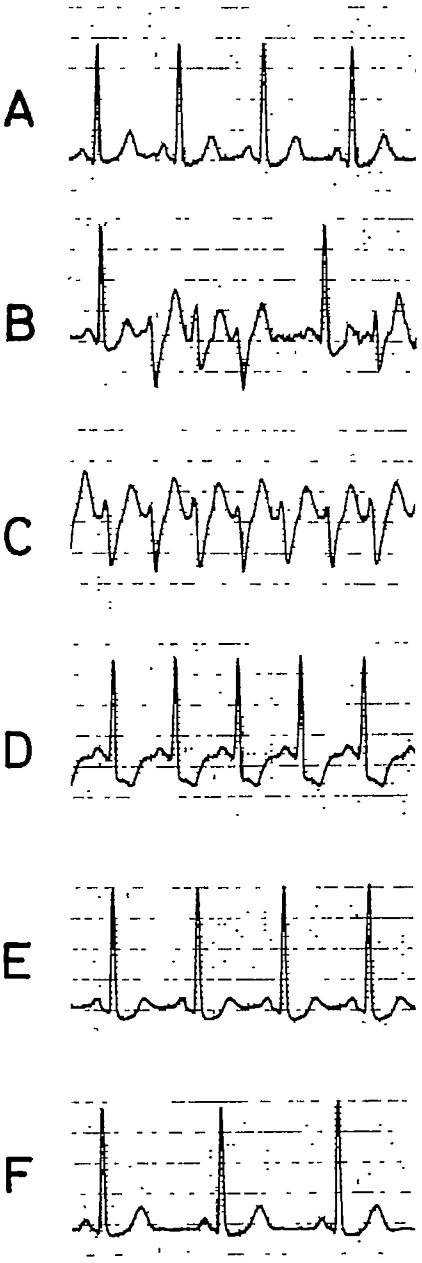


Fig 1 Electrocardiogram (lead II) before induction of spinal anaesthesia (A); immediately after administration of methylergometrine and prostaglandin $F_2\alpha$ (B and C), after administration of lidocaine (D); and 40 min and 75 min after administration of isosorbide dinitrate (E and F respectively)

1 Mathew JP, Fleisher LA, Rinehouse JA, Sevarino FB, Sinatra RS, Nelson AH, Prokop EK, Rosenbaum SH ST segment depression during labor and delivery. *Anesthesiology* 1992; **77**: 635–41

2 Palmer CM, Norris MC, Guidici MC, Leighton BL, DeSimone CA. Incidence of electrocardiographic changes during cesarean delivery under regional anesthesia. *Anesth Analg* 1990; **70**: 36–43

3 McLintic AJ, Pringle SD, Lilley S, Houston AB, Thorburn J. Electrocardiographic changes during cesarean section under regional anesthesia. *Anesth Analg* 1992; **74**: 51–6

4 Ross RM, Baker T. Cardiac enzymes in patients undergoing caesarean section. *Can J Anaesth* 1995; **42**: 46–50

5 Mukherji J, Samaddar JC. How safe is caesarean section? *J Obstet Gynaecol* 1995; **21**: 17–21

British Journal of Anaesthesia **84** (**4**): 541–545 (2000)

Book Reviews

Medicine for Anaesthetists. 4th Edn. M. D. Vickers and I. Power (editors). Published by Blackwell Science, Boston, USA. Pp. 408, indexed; illustrated. Price £79.50

The fourth edition of this familiar book arrives 10 years after the previous edition, with a newly associated editor and with two thirds of the chapters rewritten by new authors. Hence your reviewer has had to start from square one—does the book fulfil its aims, and what are its strengths and what are its weaknesses?

There are no doubts that today's anaesthetists (note the small case!) are very much part of a perioperative team, being asked to care for sicker and older patients undergoing more complex and time-consuming surgery We need, therefore, to understand the altered pathophysiology of our patients; what special pharmacological problems they present, and what are the most efficient ways to provide safe and trouble-free anaesthesia. This book takes the anaesthetist a long way down the track, with authors coming from three continents—and a number of examiners for the FRCA among them!

As with any multi-author book, there are the good bits and the not so good—among the former must be the authoritative reviews on hypertension and vascular disease by Foex and Howell; on lung disease by Campbell and Vaughan, and on neurological disorders by Frost Arterial hypertension has been correctly re-defined according to the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure—with the cut-off point clearly stated as 140/90 mm Hg. Although the authors suggest there are data to show that anaesthesia and surgery in patients with diastolic pressures greater than 120 mm Hg are associated with myocardial ischaemia, and that diastolic pressures less than 110 mm Hg are associated with no greater anaesthetic and surgical risk compared with normotensive controls, we are still awaiting the definitive statement of the actual increase in risk (from the point of view of morbidity and mortality) for a given increase in diastolic or systolic pressure. The chapter on psychiatric disorders and substance abuse by Jenkins gives a well-rounded overview of many of the problems that the anaesthetist may face.

In other chapters, the reader is left thinking why has the author not mentioned such and such—as an example, in Table 5.5, there is mention of the toxicity from pethidine in renal failure due to accumulation of norpethidine, but no comment of the adverse effects of elevated brain concentrations of morphine-6-glucuronide following morphine administration; while anaesthesia for renal transplantation is dismissed in about 200 words. Once again, the question of halothane hepatoxicity and the repeated use of halothane is touched upon and then circumvented in a less than satisfactory manner. If there is a possible immune basis for the hepatic problems, can the authors really justify the statement (page 135) that 'in countries where an alternative (to halothane) is not an option, an interval between exposures of at least 6 months, should reduce the risk'. This reviewer would argue that if there is no other option, then halothane will have to be used and the consequent time period of 6 months is based on NO FIRM OR SUBSTANTIVE EVIDENCE! The immune basis of reactions do not go away!

Similarly, if alfentanil and sufentanil are appropriate for providing analgesia for hepato-biliary surgery, why not fentanyl? The chapter on gastro-intestinal disorders offers no comment on the duration of starvation for the surgical patient (despite inclusion in the further reading list of a recent review article on that very topic by Maltby).

There are other statements which may be the ideal of perfection—but can we really achieve these on all occasions? For example, how many of us admit *all* diabetics 2–3 days before surgery; and although the authors recommend the so-called Alberti regimen (combined glucose–potassium–insulin), there are no data to show this is any better in normoglycaemic control than separate infusions of glucose and insulin (and it is certainly more time consuming) Do we really need to consider converting oral hypoglycaemic controlled type 2 diabetics to insulin prior to very minor surgery?

The editors are sadly guilty in one or two areas where greater editorial control would have improved the uniformity of the book—we are subjected to a mixture of SI and traditional units for plasma drug concentrations; and there is lack of uniformity over the referencing of each chapter—some authors have included 150–200 references (mostly from the last decade—but not always), some authors have less than 10 references, while yet others offer a list for further reading. The guidance for endocarditis prophylaxis is wisely given for both UK and American practice—but do we need the UK guidance repeated *verbatim* in both chapters 1 and 2?

Many of the chapters are well presented with tables and figures illustrating the key points. Overall the number of typographical errors is pleasingly low All this said, at the end of the day, the book is a MUST for the examination candidate There has been a real attempt to put pathophysiology, pharmacology and clinical practice together on a firm footing and in a sensible manner Every operating theatre suite should probably have a copy for the junior who is on-call and comes across a new medical problem for the first time My own copy will now return to the office-desk; it will be well thumbed by the time that the 5th edition appears!

J. W. Sear

Anesthesia for Genetic, Metabolic and Dysmorphic Syndromes of Childhood. V. C. Baum and J. E. O'Flaherty. Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 336, illustrated Price $99.00.

From time to time a book comes along which is an absolute delight to review and which fills an obvious gap in the current literature. This is such a book, and I feel certain it will be welcomed by those who like me find it impossible to remember the anaesthetic implications of all those syndromes that appear on children's operating lists. A knowledge of the potential risks of anaesthesia posed by rare syndromes is important not only in the interests of patient safety, but also to enable the anaesthetist to meet the increasing expectations of parents to be fully informed about the anaesthetic implications of their child's syndrome. In contrast to previous books, which have mostly been written by paediatricians, these authors are both doubly qualified as anaesthesiologists and paediatricians, and have first hand experience of anaesthetic practice in a variety of general hospital settings The book is primarily written for those who do not work in large paediatric centres, but will be invaluable for all who anaesthetize children Whilst most of us know about the handful of common syndromes, even full time paediatric anaesthetists would be hard-pressed to list more than a fraction of those found in this book. It is intended to be used like an encyclopaedia and for this reason there is no index, syndromes being listed in alphabetical order. Synonyms are included where appropriate and for each syndrome a brief clinical summary is provided There then follows a list of all possible findings in relation to the airway, respiratory, cardiovascular, neuromuscular, orthopaedic,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

gastrointestinal and genitourinary systems Perhaps the most valuable feature of the book is that the anaesthetic considerations are listed separately and explicitly for each syndrome, and do not have to be deduced from the list of medical problems. Anaesthetic implications are described succinctly enough to be digested at short notice, as for example before embarking on an urgent procedure, whilst all important clinical points are covered. Relevant discussions of those syndromes which persist into adult life are included, as are those syndromes without significant anaesthetic implications. Each section concludes with a brief selected bibliography, limited to references in English published after 1974. No anaesthetic plan is proposed, the authors assuming that the reader is competent enough to arrive at an appropriate plan when presented with the facts. Reports of techniques which have been successfully used in the management of individual syndromes are, however, included in the bibliography where appropriate. For those wishing to obtain further information, each syndrome is cross-referenced to the appropriate listing in the eleventh edition of McKusick's *Mendelian Inheritance in Man* (1994). Presumably this cross-referencing will become out of date if a twelfth edition of McKusick's catalogue is published.

The book is relatively sparsely illustrated and the legends of one or two illustrations do not make it clear to which syndrome they refer. Despite these relatively minor criticisms, however, the book provides an extremely comprehensive reference manual for all those involved in paediatric anaesthesia and should be made readily available in departmental libraries. The book is well produced between hard covers, and is easy to read. At $99 US, it is good value for money. Anaesthetists with a significant paediatric practice would be well advised to purchase their own copies.

D. Hatch

Handbook of Pediatric Intensive Care. 3rd Edn. M. C. Rogers and M. A. Helfaer (editors). Published by Williams and Wilkins. Pp. 994; index; illustrated. Price $49.00.

This North American text is divided into 29 chapters and its multiple authorship mean that there is some duplication of information. It is arranged in a combined organ system and disease process manner beginning with cardiopulmonary resuscitation and considering respiratory, cardiovascular, neurological, infectious diseases and multiple organ failure. There are chapters on hepatic failure and transplantation, renal, endocrine, metabolic disease and haematological disorders. Injury is subdivided into that caused by poisoning, multiple trauma, burns and inhalation. There are additional chapters on brain death, organ donation and withdrawal of life support, and pain, sedation and postoperative anaesthetic management in the PICU. There is a 69 page appendix which contains some physiological data and a basic formulary The layout of each chapter is very helpful with a heading summary of each topic covered on the first page, together with its page reference. There are line drawings, occasional photographs and summary tables which are useful throughout the text. Even though there is cross-referencing, the 53 pages of index are less helpful.

The handbook is a distillate of the *Textbook of Pediatric Intensive Care* by the same authors but with much of the physiology and pathophysiology omitted. As a handbook it remains an independent text. It contains occasional references to authors but without any means of obtaining further information. Even so, the handbook is a considerable length; too large to fit in a coat pocket.

Focusing more on the details of text, the North American paediatric resuscitation guidelines are broadly in line with those in the United Kingdom but with the predictably different terminology. However, there are errors within the text. For example, in the description of defibrillation, there is an omission of 'per kg' after Joules, although this is correct in the tables. There are also omissions in the text which are clinically important. In the description of the management of acute epiglottitis, there is no mention of the potential airway crisis which may be precipitated by separation of the child from the parent prior to inhalational induction of anaesthesia. Further details of the pathophysiology of bronchiolitis would be helpful in the management of this common condition. Although some neonatal medical conditions are covered, the intensive care management of neonatal surgical conditions is omitted. This may reflect organizational differences in paediatric *vs* neonatal intensive care in the United States but a considerable amount of pre- and post-operative neonatal surgical care falls within the remit of paediatric intensive care in the United Kingdom. The proportion of textual space given to different clinical conditions is surprising, particularly in a Handbook. A chapter of 26 pages is devoted to hepatic transplantation, a specialist procedure limited to a few paediatric intensive care centres, whereas only two pages consider the much more common paediatric intensive care aspects of the management of child abuse.

From the preface, it is difficult to understand whom the editors consider will benefit from this text. My view is that the *Handbook of Pediatric Intensive Care* will be useful for specialist registrars in their first attachment to paediatric intensive care units. In addition, any hospital anaesthetic department which is involved in the resuscitation and stabilization of critically ill children or undertakes care for children in another capacity will find this book helpful. Similarly, an accident and emergency department which receives children will find this text a useful reference book. A consultant in full-time paediatric intensive care practice who owns one or more large paediatric intensive care textbooks may find that this handbook has merits as an aide-mémoire when preparing teaching material.

J. Ratcliffe

Problems in Anesthesia Series. L. A. Fleisher and D. S. Prough (editors-in-chief). *Fluids and Electrolytes*. D. S. Prough (guest editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 134; indexed, illustrated.

This issue of *Problems in Anesthesia* was written primarily by authors from the University of Texas. In 11 chapters, relevant aspects of fluid therapy are covered. The text is easy to read and illustrated with multiple figures, tables and reference lists comprising the most relevant references. Besides some classic references, recent papers are also referenced published between 1997 and 1999 (3–31%).

The book starts by discussing kinetic principles of intravenous fluid therapy and gives a nice overview of this new concept. Haemodilution is the second chapter. Physiology and compensatory mechanisms are well covered. Particularly interesting is the discussion of the involvement of nitric oxide in the increase in cardiac output. Unfortunately, the well established haemodilution tolerance of elderly patients or patients with coronary artery disease or compromised cardiac contractility is not discussed.

The chapter on the influence of crystalloid and colloid on lung water is excellent. The strengths and weaknesses of the studies discussed are clearly described and the link between physiology and clinical practice is fabulous. Unfortunately, recent review articles and meta-analyses on colloids and albumin are not covered. The chapter on prevention of transfusions is clearly written but transfusion related immunosuppression and blood shortages are underrated. There is also an overview of blood substitutes. Although haemoglobin based oxygen carriers and perfluorocarbon emulsions are mentioned, the chapter nearly exclusively describes haemoglobin based oxygen, and does not correctly represent the current status of development in this field. In addition, the specification of perflubron, one of the perfluorocarbon emulsions is incorrect; this is a 60% w/v and not a 40% w/v emulsion.

The chapters on prehospital fluid resuscitation for trauma and hypertonic solutions are easy to follow overviews. Fluid resuscitation in burns is an excellent chapter, starting with a most interesting section on the historic development in this field. Electrolyte abnormalities are also covered adequately although chloride abnormalities and their effect on acid–base homeostasis are lacking. The effects of colloids on blood coagulation are finally summarized in a standard review type chapter. Compared with its rare clinical use, the discussion of Dextran is exaggerated and a number of new and important papers on the impact of crystalloids and colloids on blood coagulation are not referenced.

Topics not specifically addressed are the effects of fluid therapy on the brain, particularly in neurosurgery and following brain injury, and the effects of fluid therapy on splanchnic organs. All chapters are well composed resulting in little overlap. The introduction in each chapter is kept short to allow immediate discussion of the topic. Except for occasional shortcomings, this book provides excellent and up-to-date information on fluid therapy.

D. R. Spahn

Pain Clinic Manual. 2nd Edn. S. E. Abram and J. D. Haddox (editors). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 480; illustrated. Price £31.00.

This volume, as the title indicates, is a manual and is crammed full of useful information in a compact and accessible form. There are two editors and in excess of 30 contributors. Many of the contributors are clearly working colleagues of the editors, which is no doubt useful for compiling a manual which is very much to do with clinical practice rather than an authoritative text book. But it is not clear from the preface exactly who is the target audience for this book. One can assume from the extent of the material in the book that it is aimed at all those working in pain clinics which includes those with medical training as well as therapists and psychologists. With such a broad background, deciding what goes in and what is omitted from a manual is a complex task. These editors have decided to include basic background information for all the disciplines involved, so we find chapters on how to take a history and how to do a physical examination, on how to do a physiotherapy or psychology assessment, as well as the use of radiotherapy, including doses, for the treatment of cancer pain. Under the section on drugs there are basic science chapters on pharmacokinetics and pharmacodynamics which would probably be too basic for medical practitioners but may be too succinct for those who do not have medical training.

Because of the decision to include a lot of background basic information including basic science, the book does run to 480 pages which makes it rather large for a manual. It is difficult to know how valuable the basic science sections are; I found it informative to read about the background information on radiotherapy, for example The style of the book is very much that of a manual in that each chapter has lots of numbered sub-headings and then each of these sub-headings is divided into further numbered sub-sections; this does result in many lists of causes, treatments, complications etc. Whilst this may not make coherent reading, it does make for very ready access to information. The great advantage of this book is that it has a huge amount of information which is readily accessible and I found the book quite quick to read because of the easy layout.

One of the main difficulties with the book from my perspective as a practising pain clinician in the United Kingdom is that this book has got a strong bias to clinical practice in the USA. I suspect there are many differences in the way pain clinics are run on different sides of the Atlantic. First, there are a number of drugs which are not mentioned in this volume, for example tramadol and capsaicin. There was an interesting emphasis on the problem of drug addiction including an example of a formal contract for controlled substances to be signed by the patient and physician; from that point of view, I suspect that the concern about drug addiction must be greater in the USA than it is in the UK (I think very few pain clinics in this country would use such a contract). There are lists of local resources such as names and addresses of patient support groups, educational groups, action lines etc. There is also a section on billing codes and procedure codes which would not be relevant outside the USA. There are a number of other areas where the emphasis may differ; for example, under the section on back pain there is no mention of some of the evidence based material on which we would place great store in the UK, such as the Clinical Standards Advisory Group and the Royal College of General Practitioners' guidelines on back pain.

There is little attempt to provide evidence for many of the statements made or treatments proposed. None of the chapters are referenced as such, but most of them do contain a recommended reading list. Manuals do occupy a unique place in medical literature as what is described is current clinical practice. Of course not all our practice is evidence based. It has been an editorial decision not to make this an evidence-based volume and I think taken on that limitation it still represents very ready access to a lot of useful information. It would have been helpful for the editors to have discussed this to some extent in their preface, it is important that those who read this book, who are most likely to be in training in the different disciplines, should be aware that many of the current practices are not necessarily evidence based and may well not be current clinical practice in the future.

In summary I think this is a useful book. It is well put together and the editors have clearly thought a lot about what to include There is a lot of information which is readily accessible. The emphasis is clearly on practice in the USA and there may be some marked differences in the way pain clinics are run elsewhere. However, there are many strengths to this book and I would recommend it for general use in pain clinics because the access to information is excellent.

S. Dolin

Thoracic Anaesthesia: Principles and Practice. S. Ghosh and R. D Latimer (editors). Published by Butterworth Heinemann, Oxford. Pp. 335; indexed; illustrated. Price £45.00.

The stated aim of this book is 'to provide an easily readable source of information for the everyday practise of thoracic anaesthesia'. It is aimed at all levels and it is anticipated that it will be helpful in preparing lectures and tutorials.

The subject matter is broadly dealt with to the satisfaction, I am sure, of the junior anaesthetist and the new consultant. For the experienced, there is still much to be gained from this book, especially when dealing with the unfamiliar. It fulfils its aim of facilitating the preparation of material for teaching. The inclusion of *key points* tables is very helpful.

More detail is required in some areas, but of course larger texts could be sought. An example is a requirement for a pneumonectomy with the common problem of the concurrence of ischaemic heart disease. When is a patient too unfit? The answer is complex, but it revolves primarily around the function of the right ventricle. A flow diagram of the pathophysiology of right heart failure in this situation and how to influence it would have been helpful. The practising anaesthetist has to shoulder the responsibility that a declaration that a patient is unacceptable from an anaesthetic point of view deprives that patient of his only chance of long term survival Finding oneself in this position, or dealing with the occasionally frightening situation on the table 'goes with the territory'.

What this book does not do well is facilitate the acquisition of further information: it is disappointing that the text is not referenced. This omission means that those stimulated to seek more data or those disagreeing with what is said have to go through the bibliography, reach for another textbook or start from scratch on Medline. Compared with the great amount of work that has gone into the preparation of the text, a more stimulating book could have been produced for just a little more effort. The starting point for many researches have come about through seemingly innocuous statements, viewed for the first time by a fresh mind. Referencing provides an immediate starting point for the energetic and curious.

A tried-and-tested traditional format has been used, beginning with a well-written history. A different approach, starting for example with a very detailed description of the thoracic surgical patient and what his diseases do to him, would have been more stimulating. The key to better patient management is understanding the pathophysiological mechanisms involved in disease and especially the effects of surgery through the stress response. I was able to find, tucked away, only a short mention of the latter. From my own observations and those of others, attempts to reduce the onslaught of the stress response lead to tremendous gains for the patient, if only in terms of pain relief.

I disagree with the philosophy that postoperative patients are best cared for in the high dependency unit or the intensive are unit (HDU/ICU). For me, one of the greatest pleasures in anaesthesia (especially thoracic anaesthesia), is to take fairly unfit patients and by providing them with impeccable regional anaesthesia and balanced analgesia, to allow them to return to the ordinary thoracic ward. As a quality indicator, I like to use this not as any kind of macho yardstick, but I believe that ICU/HDU is positively harmful to outcomes! Facilitation of intensive monitoring requires immobility which is detrimental to the maintenance and improvement of functional residual capacity. The proximity of the ventilator can become a self-fulfilling prophecy. I may be a lone voice in this theory but it certainly makes anaesthesia more challenging and exciting by providing me with clear goals.

Because pain management (along with neuroendocrine stress modification) is central to the outcome, and is secondary in importance only to airway management, it is a shame that this chapter is in its traditional place of being tucked away almost at the back of the book. This otherwise well written script should have included a *comparison* of methods available, with intrapleural analgesia and continuous intravenous opiates occupying equal bottom. The reader should have been informed how the choice of analgesia will affect, for example, the patient's pulmonary function. The tyro may be encouraged in the analogy that the choice is of similar importance to that of one vapour over another. It is not.

Overall, I would recommend this book as a good starting place for the study of thoracic anaesthesia and it has been a pleasure to read it.

J. Richardson

Problems in Anesthesia Series. L. A. Fleisher and D. S. Prough (editors-in-chief). *Vascular Anesthesia.* J. E Ellis and M. F. Roizen (guest editors). Published by Lippincott Williams and Wilkins, Philadelphia. Pp. 286; indexed; illustrated

Although this is part of a series, it is definitely a book rather than a journal. The nine chapters cover a lot of territory and go beyond what the reader might expect, i.e. preoperative preparation, techniques of anaesthesia, etc. The book opens with a chapter on secondary prevention of coronary artery disease and later we have interesting chapters on clinical pathways, health services research and database analysis. The book itself is well bound and pleasant to handle. The individual chapters are really essays rather than classic book chapters and benefit from this approach. The authors have been given space to pursue an individual topic in depth and there are a great many references which are as up-to-date as the publication date (April 1999) can allow.

The editors have done a good job by bringing together some very different approaches to the subject area; the result is a refreshing read. I particularly enjoyed the chapters which were broad ranging; for example, 'Clinical Pathways for Vascular Anesthesia and Surgery' highlights the vastly different types of care offered by different institutions for the same type of procedure and the variability in costs and outcomes between institutions. The authors go on to identify these variations in process and outcome as appropriate areas to target for improvement. They encourage us to minimize cost whilst aiming for the best possible outcomes. An interesting discussion covers cost shifting which will be familiar to anyone trying to debate the use of expensive drugs, disposables or staffing arrangements in one part of the hospital in the hope of making savings somewhere else. How can we move forward if one department ends up spending in order to save another department's budget?

The actual process of vascular anaesthesia is comprehensively covered with detailed approach to cardiac evaluation, endovascular surgery, monitoring, haemostasis and renal protection. In each chapter, the alternatives are clearly debated and evidence (where it exists) is well referenced.

Research and Database Analysis offers a fascinating overview of the strengths (and weaknesses) of this type of research. The discussion includes the use of outcome data for individual surgeons in clinical governance and points out the pitfalls of this approach. There is useful advice on how observed disparities in outcomes can be fed back to staff in a constructive manner. We are taken through the structure/process/outcome paradigm for measuring the quality of patient care. Although these ideas are well known outside clinical circles (the approach was invented in 1966!), it was certainly new to me. For the uninitiated, *structure* refers to issues like availability of an intensive care unit; *process* might be the percentage of patients in whom a CVP line was used; and *outcomes* include morbidity, mortality, cost and patient satisfaction. There is plenty here for critical readers looking to take back new ideas to evaluate their own clinical practice.

I enjoyed this little book; its contents are timely and thought-provoking. Chunks of it are excellent reading and would assist a trainee facing a consultant appointments committee where they might be asked about broad and strategic issues in health care management rather than focusing on their own specialty There is something for everybody here, technical anaesthetists and those with a special interest in pharmacology and physiology will find plenty of detail, whilst the more free-thinking will be attracted by the quality of debate and breadth of coverage.

R. Sneyd

Anesthesia Review. M. Bowman-Howard. Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 380; indexed. Price $39.95.

Anesthesia Review attempts to provide a rapid revision of the entire subject of anaesthesia for trainees. According to the preface, its aim is to help prepare for the written and oral American board examinations. The book was originally created as part of an anaesthesiology resident education programme with reference to four major American textbooks (Millar RD *et al.* eds *Anesthesia*, 4th Edition, 1994; Barash PG, Cullen BF, Stoelting RK eds *Clinical Anesthesia*, 3rd Edn 1997; Cousins MJ, Bridenbaugh PO eds *Neural Blockade in Clinical Anesthesia and Management of*

Pain, 3rd Edn 1998; and Stoelting RK *Pharmacology and Physiology in Anesthetic Practice*, 3rd Edn 1999).

The book is divided into three main sections. The first 104 pages consist of lists of simple short questions, and are followed by 229 pages of structured answers; the remaining section contains clinical scenarios. Across these three sections the contents cover physiology, pharmacology, general and subspeciality anaesthesia (thoracic, cardiac, paediatric, obstetric, neuroanaesthesia, acute and chronic/cancer pain management), regional anaesthesia, co-existing medical disease and electrical safety.

For instance, questions in the section on 'General Aspects of Anesthesia' are divided under such subheadings as: the anesthesia machine, monitoring, patient positioning, preoperative evaluation, preoperative medications, and 'postanesthesia recovery'. 'Anesthesia Machine' is further subdivided under keywords such as: oxygen supply to the anesthesia machine, fail-safe system, flowmeters, vaporizers, Mapleson circuits, circle system, ventilators, scavenging systems and gas monitoring, and checking the anesthesia machine/humification. Questions are formulated concisely under each section, such as 'What is the Bain circuit? What are its advantages? How can ventilators be classified?'

The answer section is again mainly in list form. Basic physiological principles are explained in every subsection and certain subjects are succinctly described. Problems of thoracic anaesthesia are discussed particularly well in the respiratory anaesthesia section under such headings as: thoracic surgery; preoperative evaluation; lateral decubitus physiology; anesthetic management of one-lung ventilation; mediastinoscopy; bronchopleural fistula and empyema; lung cysts and bullae resection; tracheal resection; and postoperative management in thoracic surgery. Physiological changes of pregnancy are well detailed in the answer chapter on obstetric anaesthesia, but are followed by an all too brief discussion (only a few lines) of the advantages and disadvantages of regional anaesthesia in labour and its role in the management of the high-risk parturient. Interestingly, general anaesthesia is recommended as the technique of choice for emergency Caesarean section. The physiology and pharmacology of cute and chronic pain are concisely summarized, but somewhat surprisingly the pain-gate theory is not mentioned. Syndromes like somatization disorders, treatment of acute low-back pain, myofascial pain syndrome, reflex sympathetic dystrophy and causalgia are all considered.

The 16 clinical scenarios do help to emphasize the complexity of clinical work and provide a mental exercise when preparing for an oral examination. They discuss (again in list form) the anaesthetic implications of thoracic surgery; airway management of tonsillar bed haemorrhage, the difficult airway; abdominal aortic aneurysm repair; carotid endarterectomy, and craniotomy for meningioma. The format of the clinical scenarios is similar to a 'Short Answer Question' in the final FRCA.

Anesthesia Review is easy to read and the question/answer format helps one to discover rapidly any deficiencies in one's knowledge. As a European trainee, I am not accustomed to US measurement units, so it was a bit difficult to assimilate some of the facts, for instance, psi (instead of SI) units in the chapter about anaesthetic machines. In the respiratory answer chapter, I would have liked a flow chart of the management of difficult intubation. Amazingly, the largyngeal mask received no mention in this section, although it was considered in Miller's 4th edition of *Anesthesia* 6 yr earlier.

The book is well referenced, cross-referenced and indexed. There are some printing errors and inaccuracies, which are particularly obvious in the pharmacology answer section, such as mivacurium being described as a long-acting neuromuscular blocking agent. The doe for reversal of residual neuromuscular blockade is quoted as up to neostigmine 1 mg kg^{-1} rather than 50–100 μg kg^{-1}. In the section on regional anaesthesia, recommendation for block of the psoas muscle compartment with 400 ml of any local anaesthetic agent is concerning. The maximum total dose of bupivacaine is stated as 300 mg, but without any reference to body weight. It is an unusual characteristic of this book that, although one may enjoy reading specific chapters such as the one about acute pain, and indeed feel one has learned from it, one suddenly becomes disillusioned by the appearance of these obvious factual errors.

In spite of its limitations and lack of accuracy, I enjoyed reading *Anesthesia Review*. It has to be said, however, that it needs to be edited again before it could be fully recommended for use as an examination revision book.

G. Sidaras

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Dr J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005.

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5" PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, methods, results and conclusions, and normally should

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

be of 50–150 words. It may be used as it stands by abstracting journals.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5–7}$ or ^{5}<space>^{16} for unrelated references. When a table, figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the test as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987; 59: 14–23

Chapter in a book:

2 Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds *Acute Pain*. London. Butterworths, 1985, 155–79

Monographs:

3. Moore, DC *Regional Block*, 4th Edn. Springfield, Illinois Charles C Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly

numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131–7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with ‘z’ rather than ‘s’ spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence may also be submitted on disk. All authors must sign the accompanying submission letter.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

The *British Journal of Anaesthesia* has implemented a change in reference style. We retain the Vancouver style, but the journal name is now abbreviated, only the change in the last page number is given and no full stop ends the reference (i.e. *Br J Anaesth* 1998; **81**: 232–9)

FREE e-mail alerting service

All Oxford University Press journals offer an e-mail table of contents alerting service. You can join this to be sent the table of contents of each issue of this journal (and any other OUP journal that you select). To register, simply go to: www.oup.co.uk/jnls/tocmail, select the OUP journal/s of your choice, and enter your e-mail address to register for this free service.

stay ahead of the field

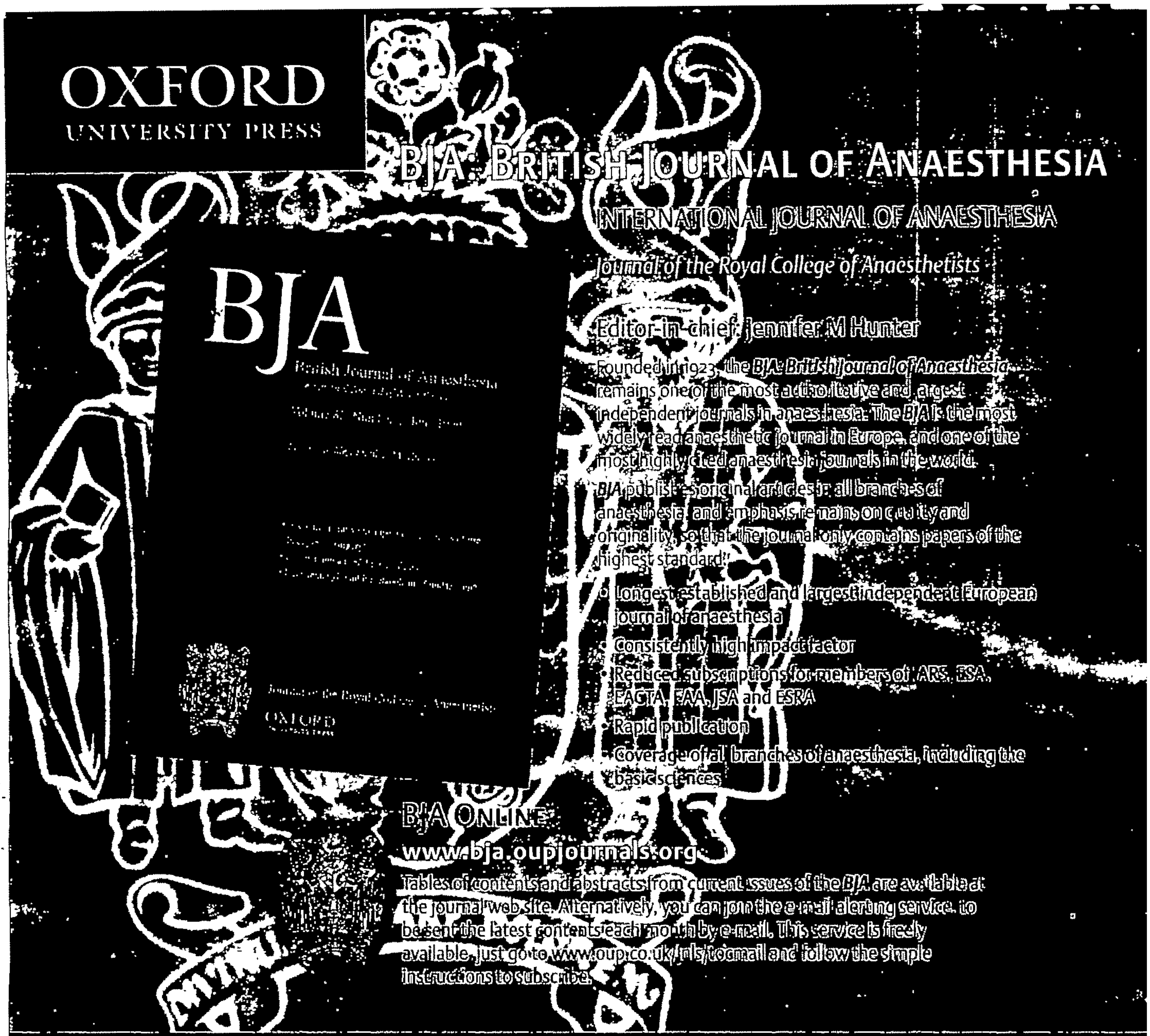
Make sure you're among the first to read the very latest research and review papers.

save time

You can browse the table of contents, and then visit the web site to read the abstracts of any papers which catch your interest, all without leaving your desk!

keep informed

You can quickly see what papers are being published across a wide range of topics.



OXFORD
UNIVERSITY PRESS

BJA: BRITISH JOURNAL OF ANAESTHESIA

INTERNATIONAL JOURNAL OF ANAESTHESIA

Journal of the Royal College of Anaesthetists

Editor-in-chief: Jennifer M Hunter

Founded in 1923, the *BJA: British Journal of Anaesthesia* remains one of the most authoritative and largest independent journals in anaesthesia. The *BJA* is the most widely read anaesthetic journal in Europe, and one of the most highly cited anaesthesia journals in the world.

BJA publishes original articles in all branches of anaesthesia, and emphasis remains on quality and originality, so that the journal only contains papers of the highest standard.

- Longest established and largest independent European journal of anaesthesia
- Consistently high impact factor
- Reduced subscriptions for members of IARS, ESA, EACTA, EAA, JSA and ESRA
- Rapid publication
- Coverage of all branches of anaesthesia, including the basic sciences

BJA ONLINE

www.bja.oupjournals.org

Tables of contents and abstracts from current issues of the *BJA* are available at the journal web site. Alternatively, you can join the e-mail alerting service, to be sent the latest contents each month by e-mail. This service is freely available, just go to www.oup.co.uk/jnls/tocmail and follow the simple instructions to subscribe.

ORDER FORM

☐ Please enter my subscription as indicated below
***BJA: British Journal of Anaesthesia*,**
ISSN 0007-0912 Volumes 84-85, 2000, 12 issues

☐ Institutions:	£217.00 / $346.00
☐ Members of IARS, JSA, EACTA, ESA, EAA, ESRA:	£105.00 / $168.00
☐ Trainees:	£105.00 / $168.00

Please note, £ Sterling applies in Europe, US$ elsewhere

OR

☐ I am interested in subscribing. Please send me a free sample copy of ***BJA: British Journal of Anaesthesia*.**

DELIVERY ADDRESS DETAILS

Name ....

Address ....

....

Postcode/Zip ....

Country ....

PAYMENT DETAILS

☐ I enclose the correct remittance
(Please make cheques payable to Oxford University Press)

☐ Please charge my Access/Visa/American Express/Mastercard/JCB

Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Expiry date ☐☐☐☐ Signature ....

If credit card address differs from delivery address, please send details.

RETURN ADDRESS

Please return your order form to: Journals Marketing, Oxford University Press, Great Clarendon Street, Oxford OX2 6DP, UK. Fax: +44 (0)1865 267835.
Subscriptions can also be placed by telephone using any major credit card. Please call the Journals Subscription Department on +44 (0)1865 267907.
E-mail: jnl.orders@oup.co.uk

In the Americas, please return to: Journals Marketing, Oxford University Press, 2001 Evans Road, Cary, NC 27513, USA. Fax: +1 919 677 1714
Subscriptions can also be placed by telephone using any major credit card. Please call the Journals Customer Services Department on 1 800 852 7323 (USA and Canada only) or +1 919 677 0977 (outside of the USA and Canada).
E-mail: jnlorders@oup-usa.org